

FILE 'HOME' ENTERED AT 10:05:37 ON 04 DEC 2001

=> fil reg

=> s lovastatin/cn or simvastatin/cn or atorvastatin/cn or cerivastatin/cn

1 LOVASTATIN/CN  
1 SIMVASTATIN/CN  
1 ATORVASTATIN/CN  
1 CERIVASTATIN/CN

L1 4 LOVASTATIN/CN OR SIMVASTATIN/CN OR ATORVASTATIN/CN OR CERIVASTATIN/CN

=> d tot

L1 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2001 ACS

RN 145599-86-6 REGISTRY

CN 6-Heptenoic acid, 7-[4-(4-fluorophenyl)-5-(methoxymethyl)-2,6-bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-, (3R,5S,6E)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 6-Heptenoic acid, 7-[4-(4-fluorophenyl)-5-(methoxymethyl)-2,6-bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-, [S-[R\*,S\*-(E)]]-

OTHER NAMES:

CN (3R,5S,6E)-7-[4-(p-Fluorophenyl)-2,6-diisopropyl-5-(methoxymethyl)-3-pyridyl]-3,5-dihydroxy-6-heptenoic acid

CN Cerivastatin

FS STEREOSEARCH

MF C26 H34 F N O5

CI COM

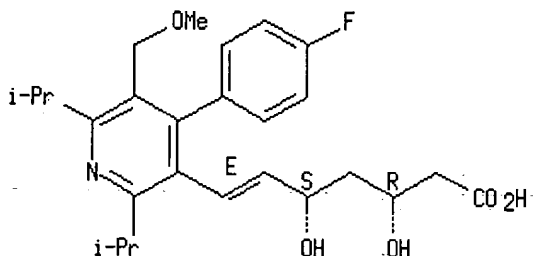
SR World Health Organization

LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, CA, CAPLUS, CBNB, CEN, CHEMCATS, CIN, CSNB, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, IPA, MRCK\*, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USAN, USPATFULL  
(\*File contains numerically searchable property data)

Other Sources: WHO

Absolute stereochemistry. Rotation (+).

Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

195 REFERENCES IN FILE CA (1967 TO DATE)

8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

196 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2001 ACS

RN 134523-00-5 REGISTRY

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, ( $\beta$ R, $\delta$ R)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, [R-(R\*,R\*)]-

OTHER NAMES:

CN ( $\beta$ R, $\delta$ R)-2-(p-Fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbonyl)pyrrole-1-heptanoic acid

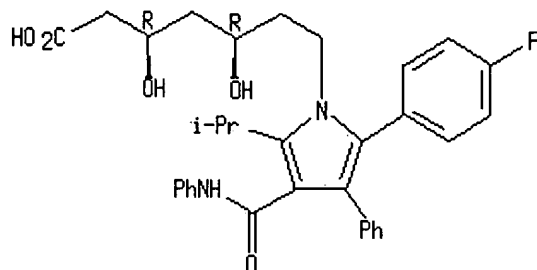
CN Atorvastatin

FS STEREOSEARCH

MF C33 H35 F N2 O5

CI COM  
 SR CA  
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS,  
 BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CEN, CHEMCATS, CIN, DDFU, DIOGENES,  
 DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK\*,  
 PHARMASEARCH, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USAN, USPATFULL  
 (\*File contains numerically searchable property data)  
 Other Sources: WHO

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

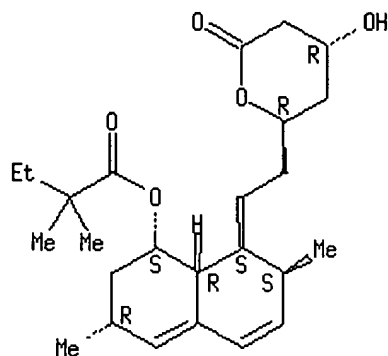
394 REFERENCES IN FILE CA (1967 TO DATE)  
 15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 396 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2001 ACS  
 RN 79902-63-9 REGISTRY  
 CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1 $\alpha$ ,3 $\alpha$ ,7 $\beta$ ,8 $\beta$ (2S\*,4S\*),8a $\beta$ ]]-

OTHER NAMES:

CN (+)-Simvastatin  
 CN L 644128-000U  
 CN MK 733  
 CN **Simvastatin**  
 CN Synvinolin  
 CN Velostatin  
 CN Zocor  
 FS STEREOSEARCH  
 DR 98609-43-9, 118607-03-7  
 MF C25 H38 O5  
 CI COM  
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*,  
 BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB,  
 CEN, CHEMCATS, CIN, CSCHM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU,  
 DRUGUPDATES, EMBASE, IFICDB, IFIUDB, IPA, MEDLINE, MRCK\*, NAPRALERT,  
 PHAR, PHARMASEARCH, PROMT, RTECS\*, SYNTHLINE, TOXCENTER, TOXLIT, USAN,  
 USPATFULL  
 (\*File contains numerically searchable property data)  
 Other Sources: WHO

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1076 REFERENCES IN FILE CA (1967 TO DATE)  
 18 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 1080 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2001 ACS

RN 75330-75-5 REGISTRY

CN Butanoic acid, 2-methyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester, (2S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Butanoic acid, 2-methyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1 $\alpha$ (R\*),3 $\alpha$ ,7 $\beta$ ,8 $\beta$ (2S\*,4S\*),8a $\beta$ ]]-

OTHER NAMES:

CN (+)-Mevinolin

CN Antibiotic MB 530B

CN L 154803

CN Lovastatin

CN Mevacor

CN Mevinolin

CN MK 803

CN Monacolin K

CN Monacolin K lactone

CN MSD 803

FS STEREOSEARCH

DR 71949-96-7, 74133-25-8, 81739-26-6

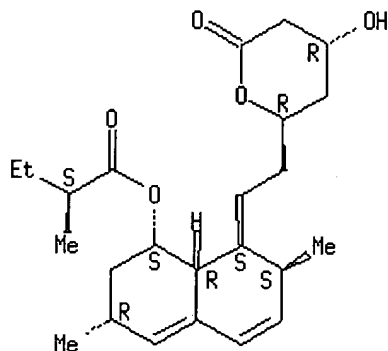
MF C24 H36 O5

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, HSDB\*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS\*, SPECINFO, SYNTHLINE, TOXCENTER, TOXLIT, USAN, USPATFULL  
 (\*File contains numerically searchable property data)

Other Sources: WHO

Absolute stereochemistry.



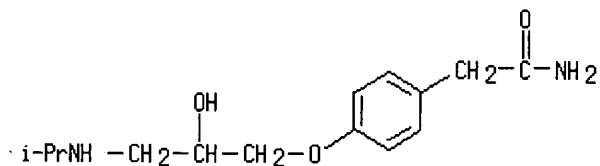
**\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\***

1422 REFERENCES IN FILE CA (1967 TO DATE)  
 51 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 1421 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s propranolol/cn or atenolol/cn  
 1 PROPRANOLOL/CN  
 1 ATENOLOL/CN  
 L2 2 PROPRANOLOL/CN OR ATENOLOL/CN

=> d tot

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2001 ACS  
 RN 29122-68-7 REGISTRY  
 CN Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]- (9CI)  
 (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Acetamide, 2-[p-[2-hydroxy-3-(isopropylamino)propoxy]phenyl]- (8CI)  
 OTHER NAMES:  
 CN (±)-Atenolol  
 CN (RS)-Atenolol  
 CN Atenolol  
 CN dl-Atenolol  
 CN DL-Atenolol  
 CN Duraatenolol  
 CN ICI 66082  
 CN Tenormin  
 FS 3D CONCORD  
 DR 106020-65-9, 60966-51-0  
 MF C14 H22 N2 O3  
 CI COM  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS,  
 BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,  
 CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU,  
 EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS,  
 NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS\*, SPECINFO, SYNTHLINE,  
 TOXCENTER, TOXLIT, USAN, USPATFULL, VETU  
 (\*File contains numerically searchable property data)  
 Other Sources: DSL\*\*, EINECS\*\*, WHO  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)

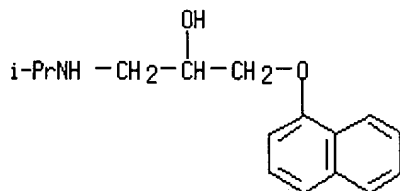


**\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\***

2250 REFERENCES IN FILE CA (1967 TO DATE)  
 14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 2256 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2001 ACS  
 RN 525-66-6 REGISTRY  
 CN 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)- (9CI) (CA  
 INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN 2-Propanol, 1-(isopropylamino)-3-(1-naphthyloxy)- (7CI, 8CI)  
 OTHER NAMES:  
 CN (±)-Propranolol  
 CN β-Propranolol  
 CN 1-(1-Naphthyloxy)-3-(isopropylamino)-2-propanol

CN 1-(Isopropylamino)-3-(1-naphthylloxy)-2-propanol  
 CN AY 64043  
 CN Betalong  
 CN DL-Propranolol  
 CN dl-Propranolol  
 CN **Propranolol**  
 CN Proprasylyt  
 CN Racemic propranolol  
 CN Reducor  
 FS 3D CONCORD  
 DR 13013-17-7  
 MF C16 H21 N O2  
 CI COM  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS,  
 BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN,  
 CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSNB, DDFU, DIOGENES, DRUGPAT,  
 DRUGU, EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*,  
 NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS\*, SPECINFO, TOXCENTER,  
 TOXLIT, ULIDAT, USAN, USPATFULL, VETU  
 (\*File contains numerically searchable property data)  
 Other Sources: EINECS\*\*, WHO  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

8896 REFERENCES IN FILE CA (1967 TO DATE)  
 102 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 8903 REFERENCES IN FILE CAPLUS (1967 TO DATE)  
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> fil medl capl biosis uspatfu;

=> s l1 or lovastatin or simvastatin or atorvastatin or cerivastatin  
 L3 13047 L1 OR LOVASTATIN OR SIMVASTATIN OR ATORVASTATIN OR CERIVASTATIN

=> s l2 or propranolol or atenolol or metoprolol  
 L4 118401 L2 OR PROPRANOLOL OR ATENOLOL OR METOPROLOL

=> s l3 and l4  
 L5 216 L3 AND L4

=> s l3 (s) l4  
 L6 103 L3 (S) L4

=> dup rem l6; focus  
 PROCESSING COMPLETED FOR L6  
 L7 96 DUP REM L6 (7 DUPLICATES REMOVED)

PROCESSING COMPLETED FOR L7  
 L8 96 FOCUS L7 1-

=> d ibib abs kwic 1-5

L8 ANSWER 1 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 91329151 MEDLINE

DOCUMENT NUMBER: 91329151 PubMed ID: 1907839

TITLE: Pharmacokinetic interaction between propranolol and the  
 HMG-CoA reductase inhibitors pravastatin and lovastatin.

AUTHOR: Pan H Y; Triscari J; DeVault A R; Smith S A; Wang-Iverson  
 D; Swanson B N; Willard D A

CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ.  
 SOURCE: BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (1991 Jun) 31 (6) 665-70.  
 Journal code: AU9; 7503323. ISSN: 0306-5251.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 (CLINICAL TRIAL)  
 Journal; Article; (JOURNAL ARTICLE)  
 (RANDOMIZED CONTROLLED TRIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199109  
 ENTRY DATE: Entered STN: 19911006  
 Last Updated on STN: 19950206  
 Entered Medline: 19910913

AB 1. Single oral 20 mg doses of the HMG-CoA reductase inhibitors pravastatin and lovastatin, with and without concomitant propranolol (40 mg twice daily), were administered to 16 healthy male subjects participating in a randomized, four-way crossover study. 2. Serum concentrations of total and active inhibitors were measured by bioassay and concentrations of pravastatin, two pravastatin metabolites and lovastatin acid were measured by gas chromatography/mass spectrometry. 3. Coadministration of propranolol with pravastatin reduced the mean area under the serum concentration-time curve (AUC) of total inhibitors by 23%, of active inhibitors by 20% and of pravastatin by 16%. 4. Coadministration of propranolol with lovastatin also resulted in decreases in the mean serum AUC of total inhibitors by 18%, of active inhibitors by 12% and of lovastatin acid by 13%. 5. These decreases in systemic drug concentrations may reflect enhanced drug first-pass hepatic clearance in the presence of propranolol. 6. The clinical significance of these changes is likely to be small.

TI Pharmacokinetic interaction between propranolol and the HMG-CoA reductase inhibitors pravastatin and lovastatin.

AB 1. Single oral 20 mg doses of the HMG-CoA reductase inhibitors pravastatin and lovastatin, with and without concomitant propranolol (40 mg twice daily), were administered to 16 healthy male subjects participating in a randomized, four-way crossover study. 2. Serum concentrations of total and active inhibitors were measured by bioassay and concentrations of pravastatin, two pravastatin metabolites and lovastatin acid were measured by gas chromatography/mass spectrometry. 3. Coadministration of propranolol with pravastatin reduced the mean area under the serum concentration-time curve (AUC) of total inhibitors by 23%, of active inhibitors by 20% and of pravastatin by 16%. 4. Coadministration of propranolol with lovastatin also resulted in decreases in the mean serum AUC of total inhibitors by 18%, of active inhibitors by 12% and of lovastatin acid by 13%. 5. These decreases in systemic drug concentrations may reflect enhanced drug first-pass hepatic clearance in the presence of propranolol. 6. The clinical significance of these changes is likely to be small.

L8 ANSWER 2 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 2001284884 MEDLINE

DOCUMENT NUMBER: 21068384 PubMed ID: 11156573

TITLE: Simvastatin inhibits noradrenaline-induced hypertrophy of cultured neonatal rat cardiomyocytes.

AUTHOR: Luo J D; Xie F; Zhang W W; Ma X D; Guan J X; Chen X

CORPORATE SOURCE: Department of Pharmacology, Guangzhou Medical College, Guangzhou 510182, China. Central Laboratory, The First Military Medical University, Guangzhou 510000, China..  
[jlucua@public.guangzhou.gd.cn](mailto:jlucua@public.guangzhou.gd.cn)

SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Jan) 132 (1) 159-64.  
 Journal code: B00; 7502536. ISSN: 0007-1188.

PUB. COUNTRY: England: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200105

ENTRY DATE: Entered STN: 20010529

Last Updated on STN: 20010529

Entered Medline: 20010524

AB 1. Oxidative mechanisms have been implicated in neonatal cardiomyocyte hypertrophy. We and others have shown that a HMG-CoA reductase inhibitor preserves endogenous antioxidant enzyme activity and inhibits cardiac hypertrophy in vivo. We therefore have examined whether noradrenaline (NA)

induces the generation of reactive oxygen species (ROS) during its induction of neonatal cardiomyocyte hypertrophy and whether **simvastatin**, a HMG-CoA reductase inhibitor, attenuates ROS production and thus NA-induced hypertrophy of cardiomyocytes. 2. NA increased the intracellular ROS levels in a concentration-dependent manner. This increase of ROS was significantly inhibited by **simvastatin** and catalase. Prazosin partially suppressed NA-induced increase of ROS and beating, while preincubation with both prazosin and **propranolol** completely abolished NA-evoked increase of ROS and beating. **Simvastatin** did not affect NA-induced increase of beating. 3. The NA-induced increase of protein content was partially suppressed by prazosin and completely abolished by preincubation with both prazosin and **propranolol**. **Simvastatin** inhibited the increase of NA-induced increase of RNA content and [(3)H]-leucine incorporation in a concentration-dependent manner. Mevalonic acid (MVA) reversed the inhibition of NA-induced RNA and protein increase by **simvastatin**. Catalase also inhibited the NA-induced increase of RNA and protein. 4. We conclude that the inhibitory effects of **simvastatin** on myocyte hypertrophy were associated with its antioxidant effects and inhibition of MVA-metabolism pathway in neonatal rat cardiomyocytes. NA-induced increases of intracellular ROS and cardiomyocyte hypertrophy requires both alpha and beta adrenoceptors activation in neonatal rat cardiomyocytes. The increases of ROS induced by NA is required for hypertrophy.

AB . . . whether noradrenaline (NA) induces the generation of reactive oxygen species (ROS) during its induction of neonatal cardiomyocyte hypertrophy and whether **simvastatin**, a HMG-CoA reductase inhibitor, attenuates ROS production and thus NA-induced hypertrophy of cardiomyocytes. 2. NA increased the intracellular ROS levels in a concentration-dependent manner. This increase of ROS was significantly inhibited by **simvastatin** and catalase. Prazosin partially suppressed NA-induced increase of ROS and beating, while preincubation with both prazosin and **propranolol** completely abolished NA-evoked increase of ROS and beating. **Simvastatin** did not affect NA-induced increase of beating. 3. The NA-induced increase of protein content was partially suppressed by prazosin and completely abolished by preincubation with both prazosin and **propranolol**. **Simvastatin** inhibited the increase of NA-induced increase of RNA content and [(3)H]-leucine incorporation in a concentration-dependent manner. Mevalonic acid (MVA) reversed the inhibition of NA-induced RNA and protein increase by **simvastatin**. Catalase also inhibited the NA-induced increase of RNA and protein. 4. We conclude that the inhibitory effects of **simvastatin** on myocyte hypertrophy were associated with its antioxidant effects and inhibition of MVA-metabolism pathway in neonatal rat cardiomyocytes. NA-induced increases. . .

L8 ANSWER 3 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 94258636 MEDLINE  
DOCUMENT NUMBER: 94258636 PubMed ID: 8199978  
TITLE: [Severe rhabdomyolysis in a patient receiving lovastatin, danazol, and doxycycline].  
Rhabdomyolyse severe chez un patient recevant lovastatine, danazol et doxycycline.  
AUTHOR: Dallaire M; Chamberland M  
CORPORATE SOURCE: Departement de medecine interne, Centre hospitalier Rouyn-Noranda, Que.  
SOURCE: CMAJ, (1994 Jun 15) 150 (12) 1991-4.  
Journal code: CVV; 9711805. ISSN: 0820-3946.  
PUB. COUNTRY: Canada  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: French  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199407  
ENTRY DATE: Entered STN: 19940714  
Last Updated on STN: 19980206  
Entered Medline: 19940707

AB Combinations of **lovastatin** and other drugs have been reported to cause rhabdomyolysis and myoglobinuria. The authors report such a case in a 72-year-old man who had been receiving **atenolol**, acetylsalicylic acid (ASA), dipyridamole, **lovastatin**, danazol, prednisone and doxycycline. The ASA, **lovastatin** and danazol were discontinued. The symptoms resolved, and laboratory test results were normal within 2 weeks. **Lovastatin** was strongly suspected; danazol was the most likely potentiator by diminishing the metabolism of **lovastatin** and its metabolites in the liver or by having a direct toxic effect on the muscles.

L8 ANSWER 4 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 2001:212586 USPATFULL  
TITLE: In vivo delivery methods and compositions  
INVENTOR(S): Kensey, Kenneth R., Malvern, PA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001044584	A1	20011122
APPLICATION INFO.:	US 2001-819924	A1	20010328 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-727950, filed on 1 Dec 2000, PENDING Continuation-in-part of Ser. No. US 2000-628401, filed on 1 Aug 2000, PENDING Continuation-in-part of Ser. No. US 2000-501856, filed on 10 Feb 2000, PENDING Continuation-in-part of Ser. No. US 1999-439795, filed on 12 Nov 1999, PENDING Continuation-in-part of Ser. No. US 1997-919906, filed on 28 Aug 1997, GRANTED, Pat. No. US 6019735		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	CAESAR, RIVISE, BERNSTEIN,, COHEN & POKOTILOW, LTD., 12TH FLOOR, SEVEN PENN CENTER, 1635 MARKET STREET, PHILADELPHIA, PA, 19103-2212		
NUMBER OF CLAIMS:	36		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	19 Drawing Page(s)		
LINE COUNT:	2120		

AB Various methods are provided for determining and utilizing the viscosity of the circulating blood of a living being over a range of shear rates for diagnostics and treatment, such as detecting/reducing blood viscosity, work of the heart, contractility of the heart, for detecting/reducing the surface tension of the blood, for detecting plasma viscosity, for explaining/counteracting endothelial cell dysfunction, for providing high and low blood vessel wall shear stress data, red blood cell deformability data, lubricity of blood, and for treating different ailments such as peripheral arterial disease in combination with administering to a living being at least one pharmaceutically acceptable agent. Agents pharmaceutically effective to regulate at least one of the aforementioned blood parameters are used to adjust distribution of a substance through the bloodstream.

DETD . . . isosorbide mononitrate, isosorbide dinitrate, nitroglycerin, hydralazine, minoxidil, hydrochlorothiazide, chlorothiazide, indapamide, metolazone, furosemide, bumetanide, ethacrynic acid, torsemide, spironolactone, triamterene, acetazolamide, mannitol, atenolol, bisoprolol, pindolol, metoprolol, timolol, nadolol, propanolol, carvedilol, captopril, fosinopril, benazepril, lisinopril, enalapril, quinapril, losartan, valsartan, eprosartan, trandolapril, fenoldopam, ramipril, doxazosin, milrinone, benidipine, lemakalim, . . . barnidipine, lacidipine, bucindolol, azelnidipine, dofetilide, ibutilide, watanidipine, lercanidipine, landiolol, telmisartan, furnidipine, azimilide, CHF 1521, valsartan/hydrochlorothiazide, enalapril/nitrendipine, sotalol, arbutamine, olmesartan, conivaptan, lovastatin, atorvastatin, cerivastatin, simvastatin, fluvastatin, cholestyramine, colestipol, clofibrate, gemfibrozil, fenofibrate, pamaqueside, pitavastatin, phentermine, phendimetrazine, sibutramine, orlistat, aspirin, warfarin, enoxaparin, heparin, low molecular weight heparin, . . .

CLM What is claimed is:

. . . isosorbide mononitrate, isosorbide dinitrate, nitroglycerin, hydralazine, minoxidil, hydrochlorothiazide, chlorothiazide, indapamide, metolazone, furosemide, bumetanide, ethacrynic acid, torsemide, spironolactone, triamterene, acetazolamide, mannitol, atenolol, bisoprolol, pindolol, metoprolol, timolol, nadolol, propanolol, carvedilol, captopril, fosinopril, benazepril, lisinopril, enalapril, quinapril, losartan, valsartan, eprosartan, trandolapril, fenoldopam, ramipril, doxazosin, milrinone, benidipine, lemakalim, . . . barnidipine, lacidipine, bucindolol, azelnidipine, dofetilide, ibutilide, watanidipine, lercanidipine, landiolol, telmisartan, furnidipine, azimilide, CHF 1521, valsartan/hydrochlorothiazide, enalapril/nitrendipine, sotalol, arbutamine, olmesartan, conivaptan, lovastatin, atorvastatin, cerivastatin, simvastatin, fluvastatin, cholestyramine, colestipol, clofibrate, gemfibrozil, fenofibrate, pamaqueside, pitavastatin, phentermine, phendimetrazine,



sibutramine, orlistat, aspirin, warfarin, enoxaparin, heparin, low  
molecular weight heparin, . . .

L8 ANSWER 5 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 94256376 MEDLINE  
DOCUMENT NUMBER: 94256376 PubMed ID: 8198018  
TITLE: Clinical implications of the biopharmaceutical properties  
of fluvastatin.  
AUTHOR: Deslypere J P  
CORPORATE SOURCE: Department of Internal Medicine, University Hospital, Gent,  
Belgium.  
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, (1994 May 26) 73 (14)  
12D-17D.  
Journal code: 3DQ; 0207277. ISSN: 0002-9149.  
PUB. COUNTRY: United States  
(CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199406  
ENTRY DATE: Entered STN: 19940707  
Last Updated on STN: 19940707  
Entered Medline: 19940629

AB Fluvastatin sodium (Lescol; Sandoz) the first entirely synthetic  
3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor  
studied, is structurally distinct from the other HMG-CoA reductase  
inhibitors currently available, all of which are fungal metabolites and  
analogues of compactin. Fluvastatin's distinct structure may be  
responsible for the biopharmaceutical properties that result in its low  
systemic exposure and, subsequently, low incidence of peripheral adverse  
events, such as headache and myositis. Fluvastatin is rapidly absorbed  
from the gastrointestinal tract; has a 30-minute half-life, the shortest  
of any currently available HMG-CoA reductase inhibitor (lovastatin, 15  
hours; pravastatin, 2 hours; simvastatin, 15.6 hours); is highly  
selective for the liver, undergoing extensive first-pass metabolism; has  
no active circulating metabolites; and does not penetrate the blood-brain  
barrier, unlike lovastatin and simvastatin. The low systemic exposure  
suggests that the occurrence of peripheral adverse events, such as  
myositis, central nervous system effects, and drug-drug interactions, may  
be less than what is currently observed with other HMG-CoA reductase  
inhibitors. Neither niacin nor propranolol had an effect on fluvastatin  
plasma levels when combined with fluvastatin. In contrast to other HMG-CoA  
reductase inhibitors, fluvastatin in combination with niacin resulted in  
no instances of myositis or other serious adverse events. Although the  
interaction of fluvastatin with cholestyramine resulted in a lower rate  
and extent of fluvastatin bioavailability, this reduction had no impact on  
clinical efficacy. Fluvastatin administered to patients chronically  
receiving digoxin had no effect on the area under the curve (AUC) of  
digoxin compared with controls. (ABSTRACT TRUNCATED AT 250 WORDS)

=> d ibib abs kwic 6-10

L8 ANSWER 6 OF 96 CAPLUS COPYRIGHT 2001 ACS

Full-text

ACCESSION NUMBER: 2001:762853 CAPLUS  
DOCUMENT NUMBER: 135:308923  
TITLE: Formulation for the prevention of cardiovascular  
disease  
INVENTOR(S): Wald, Nicholas J.; Law, Malcolm R.  
PATENT ASSIGNEE(S): UK  
SOURCE: PCT Int. Appl., 76 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001076632	A1	20011018	WO 2001-GB1618	20010410
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,				

LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,  
 RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,  
 VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-8791 A 20000410  
 GB 2001-548 A 20010109

AB A method for the prevention of cardiovascular disease is administration of a combination of active principals for use in the prevention of cardiovascular disease, notably ischemic heart disease (including heart attacks) and stroke among the general adult population. Compns. contain, e.g., hydrochlorothiazide, atenolol, and enalapril as blood pressure lowering agents, atorvastatin as a lipid-regulating agent, aspirin as a platelet function altering agent, and folic acid as a serum homocysteine lowering agent.

REFERENCE COUNT: 4

REFERENCE(S): (1) Neutel, J; AMERICAN JOURNAL OF HYPERTENSION 1999, V12(8 PT 2), P73S MEDLINE  
 (2) Rhymer, P; WO 9811896 A 1998 CAPLUS  
 (3) Squibb Bristol Myers Co; WO 9819690 A 1998 CAPLUS  
 (4) Tobert, J; WO 9738694 A 1997 CAPLUS

L8 ANSWER 7 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 2000:174799 USPATFULL

TITLE: Biodegradable polymers chain-extended by phosphates, compositions, articles and methods for making and using the same

INVENTOR(S): Mao, Hai-Quan, Towson, MD, United States  
 Leong, Kam W., Ellicott City, MD, United States  
 Zhao, Zhong, Baltimore, MD, United States  
 English, James P., Chelsea, AL, United States

PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., Baltimore, MD, United States (U.S. corporation)  
 Johns Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6166173		20001226
APPLICATION INFO.:	US 1998-53649		19980402 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-832217, filed on 3 Apr 1997, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Merriam, Andrew E. C.		
NUMBER OF CLAIMS:	260		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	17 Drawing Figure(s); 14 Drawing Page(s)		
LINE COUNT:	2164		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Biodegradable polymers are described comprising the recurring monomeric units shown in formula I or II: wherein X is --O-- or --NR'--, where R' is H or alkyl; L is a branched or straight chain aliphatic group having from 1-20 carbon atoms; M and M are each independently (1) a branched or straight chain aliphatic group having from 1-20 carbon atoms; or (2) a branched or straight chain, oxy-, carboxy- or amino-aliphatic group having from 1-20 carbon atoms; Y is --O-- or --NR'--, where R' is H or alkyl; R is H, alkyl, alkoxy, aryl, aryloxy, heterocyclic or heterocycloxy; the molar ratio of x:y is about 1; the molar ratio n:(x or y) is between about 200:1 and 1:200; and the molar ratio q:r is between about 1:99 and 99:1; wherein said biodegradable polymer is biocompatible before and upon biodegradat.

Processes for preparing the polymers, compositions containing the polymers and biologically active substances, articles useful for implantation or injection into the body fabricated from the compositions, and methods for controllably releasing biologically active substances using the polymers, are also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . as pilocarpine; (32) cholinesterase inhibitor  
 parasympathomimetics, such as pyridostigmine; (33)  $\alpha$ -blocker  
 sympatholytics, such as prazosin; (34)  $\beta$ -blocker sympatholytics,

such as atenolol; (35) adrenergic agonist sympathomimetics, such as albuterol and dobutamine; (36) cardiovascular agents, such as aspirin (ASA) (enteric coated ASA); (37)  $\beta$ -blocker antianginals, such as atenolol and propranolol; (38) calcium-channel blocker antianginals, such as nifedipine and verapamil; (39) nitrate antianginals, such as isosorbide dinitrate (ISDN); (40) cardiac glycoside. . . as digoxin; (41) class I antiarrhythmics, such as lidocaine, mexiletine, phenytoin, procainamide, and quinidine; (42) class II antiarrhythmics, such as atenolol, metoprolol, propranolol, and timolol; (43) class III antiarrhythmics, such as amiodarone; (44) class IV antiarrhythmics, such as diltiazem and verapamil; (45)  $\alpha$ -blocker. . . such as prazosin; (46) angiotensin-converting enzyme inhibitor (ACE inhibitor) antihypertensives, such as captopril and enalapril; (47)  $\beta$ -blocker antihypertensives, such as atenolol, metoprolol, nadolol, and propranolol; (48) calcium-channel blocker antihypertensive agents, such as diltiazem and nifedipine; (49) central-acting adrenergic antihypertensives, such as clonidine and methyldopa; (50). . . such as gemfibrozil and probucol; (53) bile acid sequestrant antilipemics, such as cholestyramine; (54) HMG-CoA reductase inhibitor antilipemics, such as lovastatin and pravastatin; (55) inotropes, such as amrinone, dobutamine, and dopamine; (56) cardiac glycoside inotropes, such as digoxin; (57) thrombolytic agents. . .

L8 ANSWER 8 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 2001569449 IN-PROCESS  
DOCUMENT NUMBER: 21530697 PubMed ID: 11675864  
TITLE: Nightmares and sleep disturbances with simvastatin and metoprolol.  
AUTHOR: Boriani G; Biffi M; Strocchi E; Branzi A  
SOURCE: ANNALS OF PHARMACOTHERAPY, (2001 Oct) 35 (10) 1292.  
Journal code: BBX; 9203131. ISSN: 1060-0280.  
PUB. COUNTRY: United States  
Letter  
LANGUAGE: English  
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals  
ENTRY DATE: Entered STN: 20011029  
Last Updated on STN: 20011029  
TI Nightmares and sleep disturbances with simvastatin and metoprolol.

L8 ANSWER 9 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 1998454162 MEDLINE  
DOCUMENT NUMBER: 98454162 PubMed ID: 9780877  
TITLE: In the past 12 to 18 months, my level of anxiety has increased significantly. I have been on atenolol and simvastatin (Zocor) for the past couple of years. Is there anything in these drugs that could cause this anxiety?..  
AUTHOR: Lee T H  
SOURCE: HARVARD HEART LETTER, (1998 Oct) 9 (2) 8.  
Journal code: C2Z; 9425723. ISSN: 1051-5313.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: K  
ENTRY MONTH: 199810  
ENTRY DATE: Entered STN: 19990106  
Last Updated on STN: 19990106  
Entered Medline: 19981029  
TI In the past 12 to 18 months, my level of anxiety has increased significantly. I have been on atenolol and simvastatin (Zocor) for the past couple of years. Is there anything in these drugs that could cause this anxiety?..

L8 ANSWER 10 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS

Full-text

ACCESSION NUMBER: 2001:550112 BIOSIS  
DOCUMENT NUMBER: PREV200100550112  
TITLE: Nightmares and sleep disturbances with simvastatin and metoprolol.  
AUTHOR(S): Boriani, Giuseppe (1); Biffi, Mauro; Strocchi, Enrico; Branzi, Angelo  
CORPORATE SOURCE: (1) Policlinico S. Orsola, Institute of Cardiology, University of Bologna, Via Massarenti 9, 40138, Bologna:

cardiol@almadns.unibo.it Italy  
 SOURCE: Annals of Pharmacotherapy, (October, 2001) Vol. 35, No. 10,  
 pp. 1292. print.  
 ISSN: 1060-0280.  
 DOCUMENT TYPE: Article; Letter  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 TI Nightmares and sleep disturbances with simvastatin and metoprolol.

=> d ibib abs kwic 11-15

L8 ANSWER 11 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS

Full-text

ACCESSION NUMBER: 1999:131259 BIOSIS  
 DOCUMENT NUMBER: PREV199900131259  
 TITLE: Effects of hypolipemic therapy on the pharmacokinetics of  
 propranolol.  
 AUTHOR(S): Wojcicki, Jerzy (1); Sterna, Rozalia; Sulzyc-Bielicka,  
 Violetta; Gawronska-Szklarz, Barbara; Drozdziak, Marek;  
 Musial, Heros David  
 CORPORATE SOURCE: (1) Dep. Pharamcol. Toxicol., Pomeranian Med. Acad.,  
 Powstancow Wlkp. 72, 70-111 Szczecin Poland  
 SOURCE: Current Therapeutic Research, (Jan., 1999) Vol. 60, No. 1,  
 pp. 20-30.  
 ISSN: 0011-393X.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English

AB The pharmacokinetics of **propranolol** was studied in 34 patients with  
 hyperlipidemia before and after a 30-day course of hypolipemic therapy.  
 Based on their diagnosis, the patients were separated into  
 hypercholesterolemic, hypertriglyceridemic, and mixed-form hyperlipidemic  
 groups. Pharmacokinetic studies were performed at the onset of the study  
 and after 30 days of treatment with **lovastatin** (hypercholesterolemic and  
 mixed-form hyperlipidemic patients) or **bezafibrate** (hypertriglyceridemic  
 patients). **Propranolol** 80 mg was given orally as a single dose before  
 and after hypolipemic therapy, and blood serum was sampled during the 24  
 hours after drug administration. Effective hypolipemic therapy has been  
 shown to induce changes in the pharmacokinetics of **propranolol**,  
 depending on the type of lipid metabolic disturbance. The most pronounced  
 alterations, such as an increase in volume of distribution, were observed  
 in patients with hypertriglyceridemia. Hypercholesterolemic therapy did  
 not significantly affect the pharmacokinetics of **propranolol**.

L8 ANSWER 12 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 2001:214666 USPATFULL  
 TITLE: Biodegradable terephthalate polyester-poly (phosphate)  
 polymers, compositions, articles, and methods for  
 making and using the same  
 INVENTOR(S): Mao, Hai-Quan, Towson, MD, United States  
 Leong, Kam W., Ellicott City, MD, United States  
 Dang, Wenbin, Baltimore, MD, United States  
 Lo, Hungnan, Shaker Heights, OH, United States  
 Zhao, Zhong, Baltimore, MD, United States  
 Nowotnik, David P., Kingsville, MD, United States  
 English, James P., Chelsea, AL, United States  
 PATENT ASSIGNEE(S): Guilford Pharmaceuticals, Inc., Baltimore, MD, United  
 States (U.S. corporation)  
 Johns Hopkins University, Baltimore, MD, United States  
 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6322797	B1	20011127
APPLICATION INFO.:	US 1998-53648		19980402 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-832215, filed on 3 Apr 1997, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Truong, Duc		
LEGAL REPRESENTATIVE:	Foley, Hoag & Eliot LLP		
NUMBER OF CLAIMS:	126		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	19 Drawing Figure(s); 15 Drawing Page(s)		

LINE COUNT: 1946

AB Biodegradable terephthalate polymers are described comprising the recurring monomeric units shown in formula I: ##STR1##

wherein R is a divalent organic moiety;

R' is an aliphatic, aromatic or heterocyclic residue;

x is  $\geq 1$ ; and

n is 0-5,000,

wherein the biodegradable polymer is biocompatible before and upon biodegradation.

Processes for preparing the polymers, compositions containing the polymers and biologically active substances, articles useful for implantation or injection into the body fabricated from the compositions, and methods for controllably releasing biologically active substances using the polymers, are also described.

DETD . . . as pilocarpine; (32) cholinesterase inhibitor parasympathomimetics, such as pyridostigmine; (33)  $\alpha$ -blocker sympatholytics, such as prazosin; (34)  $\beta$ -blocker sympatholytics, such as atenolol; (35) adrenergic agonist sympathomimetics, such as albuterol and dobutamine; (36) cardiovascular agents, such as aspirin (ASA) (enteric coated ASA); (37)  $\beta$ -blocker antianginals, such as atenolol and propranolol; (38) calcium-channel blocker antianginals, such as nifedipine and verapamil; (39) nitrate antianginals, such as isosorbide dinitrate (ISDN); (40) cardiac glycoside. . . as digoxin; (41) class I antiarrhythmics, such as lidocaine, mexiletine, phenytoin, procainamide, and quinidine; (42) class II antiarrhythmics, such as atenolol, metoprolol, propranolol, and timolol; (43) class III antiarrhythmics, such as amiodarone; (44) class IV antiarrhythmics, such as diltiazem and verapamil; (45)  $\alpha$ -blocker. . . such as prazosin; (46) angiotensin-converting enzyme inhibitor (ACE inhibitor) antihypertensives, such as captopril and enalapril; (47)  $\beta$ -blocker antihypertensives, such as atenolol, metoprolol, nadolol, and propranolol; (48) calcium-channel blocker antihypertensive agents, such as diltiazem and nifedipine; (49) central-acting adrenergic antihypertensives, such as clonidine. . . such as gemfibrozil and probucol; (53) bile acid sequestrant antilipemics, such as cholestyramine; (54) HMG-CoA reductase inhibitor antilipemics, such as lovastatin and pravastatin; (55) inotropes, such as amrinone, dobutamine, and dopamine; (56) cardiac glycoside inotropes, such as digoxin; (57) thrombolytic agents, . . .

L8 ANSWER 13 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 2000:160610 USPATFULL

TITLE: Biodegradable terephthalate polyester-poly (phosphonate) compositions, articles, and methods of using the same

INVENTOR(S): Mao, Hai-guan, Towson, MD, United States  
Leong, Kam W., Ellicott City, MD, United States  
Zhao, Zhong, Ellicott City, MD, United States  
Dang, Wenbin, Ellicott City, MD, United States  
English, James P., Chelsea, AL, United States  
Nowotnik, David P., Kingsville, MD, United States  
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., Baltimore, MD, United States (U.S. corporation)  
Johns Hopkins University School of Medicine, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6153212		20001128
APPLICATION INFO.:	US 1998-165375		19981002 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Azpuru, Carlos A.		
LEGAL REPRESENTATIVE:	Howrey Simon Arnold & White, LLP		
NUMBER OF CLAIMS:	59		
EXEMPLARY CLAIM:	1		

NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)

LINE COUNT: 1448

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A medical device is described comprising a biodegradable terephthalate copolymer comprising the recurring monomeric units shown in formula I below: ##STR1## wherein R is a divalent organic moiety; R' is an aliphatic, aromatic, or heterocyclic residue; x is  $\geq 1$ ; and n is 3-7,500, and where the biodegradable terephthalate copolymer is sufficiently pure to be biocompatible and is capable of forming biocompatible residues upon biodegradation. In addition, compositions containing the copolymers and biologically active substances, articles useful for implantation or injection into the body fabricated from the compositions, and methods for controllably releasing biologically active substances using the copolymers, are also described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . as pilocarpine; (32) cholinesterase inhibitor parasympathomimetics, such as pyridostigmine; (33)  $\alpha$ -blocker sympatholytics, such as prazosin; (34)  $\beta$ -blocker sympatholytics, such as atenolol; (35) adrenergic agonist sympathomimetics, such as albuterol and dobutamine; (36) cardiovascular agents, such as aspirin (ASA) (enteric coated ASA); (37)  $\beta$ -blocker antianginals, such as atenolol and propranolol; (38) calcium-channel blocker anti-anginals, such as nifedipine and verapamil; (39) nitrate antianginals, such as isosorbide dinitrate (ISDN); (40) cardiac glycoside. . . as digoxin; (41) class I antiarrhythmics, such as lidocaine, mexiletine, phenytoin, procainamide, and quinidine; (42) class II antiarrhythmics, such as atenolol, metoprolol, propranolol, and timolol; (43) class III antiarrhythmics, such as amiodarone; (44) class IV antiarrhythmics, such as diltiazem and verapamil; (45)  $\alpha$ -blocker. . . such as prazosin; (46) angiotensin-converting enzyme inhibitor (ACE inhibitor) antihypertensives, such as captopril and enalapril; (47)  $\beta$ -blocker antihypertensives, such as atenolol, metoprolol, nadolol, and propranolol; (48) calcium-channel blocker antihypertensive agents, such as diltiazem and nifedipine; (49) central-acting adrenergic antihyper-tensives, such as clonidine. . . such as gemfibrozil and probucol; (53) bile acid sequestrant anti-lipemics, such as cholestyramine; (54) HMG-COA reductase inhibitor anti-lipemics, such as lovastatin and pravastatin; (55) inotropes, such as amrinone, dobutamine, and dopamine; (56) cardiac glycoside inotropes, such as digoxin; (57) thrombolytic agents, . . .

L8 ANSWER 14 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 1999:170710 USPATFULL

TITLE: Two-stage solution polymerization of high molecular weight poly(phosphoesters)

INVENTOR(S): Zhao, Zhong, Ellicott City, MD, United States  
Mao, Hai-quan, Towson, MD, United States  
Leong, Kam W., Ellicott City, MD, United States

PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., Baltimore, MD, United States (U.S. corporation)  
Johns Hopkins University, Baltimore, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6008318		19991228
APPLICATION INFO.:	US 1998-98620		19980617 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1997-877624, filed on 18 Jun 1997, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Truong, Duc		
LEGAL REPRESENTATIVE:	Howrey & Simon		
NUMBER OF CLAIMS:	38		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)		
LINE COUNT:	1244		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A process for making a phosphoester polymer comprising the recurring monomeric units of formula I: ##STR1## wherein: X is --O-- or --NR"--, where R" is H or alkyl;

L is a divalent organic moiety;

R' is H, alkyl, alkoxy, aryl, aryloxy, heterocyclic, or heterocycloxy;  
and

n is between about 25 to 2,000,

is described. The process comprises the steps of:

(a) polymerizing in the presence of a solvent p moles of a di-XH compound having formula II:

H--X--L--X--H

II

wherein X and L are as defined above, with q moles, where  $p \approx q$ , of a phosphorodihalo compound to form a polymer of formula I, wherein n is about 12 to 1000, having a first molecular weight  $M_w$ , wherein the solvent is present in an amount greater than about 5 ml of solvent per gram of compound of formula II;

(b) removing at least about 25% of the solvent to form a more concentrated reaction mixture; and

(c) further polymerizing the concentrated reaction mixture for an additional time sufficient to produce a polymer of formula I wherein n is between about 25 and 2,000, the polymer having a second molecular weight  $M_w$ , which is significantly higher than  $M_w$ .

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . as pilocarpine; (32) cholinesterase inhibitor  
parasymphomimetics, such as pyridostigmine; (33)  $\alpha$ -blocker  
sympatholytics, such as prazosin; (34)  $\beta$ -blocker sympatholytics,  
such as atenolol; (35) adrenergic agonist sympathomimetics, such as  
albuterol and dobutamine; (36) cardiovascular agents, such as aspirin  
(ASA) (enteric coated ASA); (37)  $\beta$ -blocker antianginals, such as  
atenolol and propranolol; (38) calcium-channel blocker antianginals,  
such as nifedipine and verapamil; (39) nitrate antianginals, such as  
isosorbide dinitrate (ISDN); (40) cardiac glycoside. . . as digoxin;  
(41) class I antiarrhythmics, such as lidocaine, mexiletine, phenytoin,  
procainamide, and quinidine; (42) class II antiarrhythmics, such as  
atenolol, metoprolol, propranolol, and timolol; (43) class III  
antiarrhythmics, such as amiodarone; (44) class IV antiarrhythmics, such  
as diltiazem and verapamil; (45)  $\alpha$ -blocker. . . such as  
prazosin; (46) angiotensin-converting enzyme inhibitor (ACE inhibitor)  
antihypertensives, such as captopril and enalapril; (47)  $\beta$ -blocker  
antihypertensives, such as atenolol, metoprolol, nadolol, and  
propranolol; (48) calcium-channel blocker antihypertensive agents, such  
as diltiazem and nifedipine; (49) central-acting adrenergic  
antihypertensives, such as clonidine. . . such as gemfibrozil and  
probucol; (53) bile acid sequestrant antilipemics, such as  
cholestyramine; (54) HMG-CoA reductase inhibitor antilipemics, such as  
lovastatin and pravastatin; (55) inotropes, such as amrinone,  
dobutamine, and dopamine; (56) cardiac glycoside inotropes, such as  
digoxin; (57) thrombolytic agents, . . .

L8 ANSWER 15 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 1999:110440 USPATFULL  
TITLE: Solution polymerization of high molecular weight  
poly(phosphoesters) in toluene  
INVENTOR(S): Zhao, Zhong, Towson, MD, United States  
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., Baltimore, MD, United  
States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5952451		19990914
APPLICATION INFO.:	US 1998-102813		19980623 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-884382, filed on 27 Jun 1997		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Mosley, Terressa		

LEGAL REPRESENTATIVE: Nath & Associates, Nath, Gary M., Drost, Patricia M.  
NUMBER OF CLAIMS: 46  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)  
LINE COUNT: 1148

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A process for making a high molecular weight poly(phosphoester)  
composition comprising:

(i) a biologically active substance; and

(ii) a poly(phosphoester) with the recurring monomeric units: ##STR1##  
wherein X is --O-- or --NR"--, where R" is H or alkyl; L is a divalent  
organic moiety, with the proviso that L cannot have the formula ##STR2##  
R' is H, alkyl, alkoxy, aryl, aryloxy, heterocyclic, or heterocycloxy;  
and n is from about 25 to 2000,

is described. The process comprises the steps of:

(a) substantially dissolving p moles of a di--XH compound in a solvent  
comprising more than 75% toluene at a first temperature between about  
-75° C. and +60° C. to form a reaction mixture;

(b) while maintaining the reaction mixture at the first temperature,  
adding q moles, where p≈q, of a phosphorodihalo compound;

(c) gradually increasing said first temperature at a rate of less than  
about 1.5° C. per minute as necessary to achieve a second  
temperature between about 0° C. and 150° C., and mixing  
the reaction mixture at the second temperature to form the polymer of  
formula I; and

(d) isolating the polymer of formula I.

(e) incorporating the biologically active substance into the polymer of  
formula I.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DRWD . . . as pilocarpine; (32) cholinesterase inhibitor  
parasympathomimetics, such as pyridostigmine; (33) α-blocker  
sympatholytics, such as prazosin; (34) β-blocker sympatholytics,  
such as atenolol; (35) adrenergic agonist sympathomimetics, such as  
albuterol and dobutamine; (36) cardiovascular agents, such as aspirin  
(ASA) (enteric coated ASA); (37) β-blocker antianginals, such as  
atenolol and propranolol; (38) calcium-channel blocker antianginals,  
such as nifedipine and verapamil; (39) nitrate antianginals, such as  
isosorbide dinitrate (ISDN); (40) cardiac glycoside. . . as digoxin;  
(41) class I antiarrhythmics, such as lidocaine, mexiletine, phenytoin,  
procainamide, and quinidine; (42) class II antiarrhythmics, such as  
atenolol, metoprolol, propranolol, and timolol; (43) class III  
antiarrhythmics, such as amiodarone; (44) class IV antiarrhythmics, such  
as diltiazem and verapamil; (45) α-blocker. . . such as  
prazosin; (46) angiotensin-converting enzyme inhibitor (ACE inhibitor)  
antihypertensives, such as captopril and enalapril; (47) 9-blocker  
antihypertensives, such as atenolol, metoprolol, nadolol, and  
propanolol; (48) calcium-channel blocker antihypertensive agents, such  
as diltiazem and nifedipine; (49) central-acting adrenergic  
antihypertensives, such as clonidine. . . such as gemfibrozil and  
probucol; (53) bile acid sequestrant antilipemics, such as  
cholestyramine; (54) HMG-CoA reductase inhibitor antilipemics, such as  
lovastatin and pravastatin; (55) inotropes, such as amrinone,  
dobutamine, and dopamine; (56) cardiac glycoside inotropes, such as  
digoxin; (57) thrombolytic agents. . .

=> d ibib abs kwic 16-20

L8 ANSWER 16 OF 96 USPATFULL

Full-text

ACCESSION NUMBER: 96:43387 USPATFULL

TITLE: Biodegradable controlled release flash flow melt-spun  
delivery system

INVENTOR(S): Fuisz, Richard C., Great Falls, VA, United States

PATENT ASSIGNEE(S): Fuisz Technologies Ltd., Chantilly, VA, United States



(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5518730		19960521
APPLICATION INFO.:	US 1992-893238		19920603 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Webman, Edward J.		
LEGAL REPRESENTATIVE:	Hoffmann & Baron		
NUMBER OF CLAIMS:	28		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	1072		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Biodegradable controlled release delivery systems using melt-spun biodegradable polymers as carriers for bio-effecting agents such as pharmaceutical actives are disclosed. Oral dosage forms as well as implants are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . allantoin; aloe; aluminum acetate, carbonate, chlorohydrate, hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; atenolol; bacitracin; balsam peru; BCNU (carmustine) beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; bethanechol; biotin; bisacodyl; bornyl acetate; bromopheniramine maleate; . . . insulin; iodine; ipecac; iron; isoxicam; ketamine; koalin; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix; lovastatin; luteinizing hormone; LHRH (luteinizing hormone releasing hormone); magnesium carbonate, hydroxide, salicylate, trisilicate; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methyl nicotinate; methyl salicylate; methylcellulose; methsuximide; metronidazole and its hydrochloride; metoprolol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its sodium salt; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerin; . . .

CLM What is claimed is:

. . . aloe, aluminum acetate, aluminum carbonate, aluminum chlorohydrate, aluminum hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, . . . sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, magnesium carbonate, magnesium hydroxide, magnesium salicylate, magnesium trisilicate, mefenamic acid, meclofenamic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine mandelate, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen sodium, nifedipine, neomycin sulfate, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, . . .

. . . isopropanol, allantoin, aloe, aluminum acetate, aluminum carbonate, chlorohydrate, hydroxide, alprozolam, amino acids, aminobenzoic acid, amoxicillin, ampicillin, amsacrine, amsalog, anethole, aspartame, atenolol, bacitracin, balsam peru, beclomethasone dipropionate, benzocaine, benzoic acid, benzophenones, benzoyl peroxide, biotin, bisacodyl, bornyl acetate, bromopheniramine maleate, buspirone, caffeine, calamine, . . . sulfate, ibuprofen, indomethacin, inositol, insulin, iodine, ipecac, iron, isoxicam, ketamine, koalin, lactic acid, lanolin, lecithin, lidocaine, lidocaine hydrochloride, lifinopril, liotrix, lovastatin, magnesium carbonate, magnesium hydroxide, salicylate, magnesium trisilicate, mefenamic acid, meclofenamic acid, meclofenamate sodium, medroxyprogesterone acetate, methenamine mandelate, menthol, meperidine hydrochloride, metaproterenol sulfate, methyl nicotinate, methyl salicylate, methylcellulose, methsuximide, metromidazole, metromidazole hydrochloride, metoprolol tartrate, miconazole nitrate, mineral oil, minoxidil, morphine, naproxen, naproxen

sodium, nifedipine, neomycin sulfate, niacin, niacinamide, nicotine, nicotinamide, nitroglycerin, nonoxynol-9, norethindone, . . .

L8 ANSWER 17 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 2000173010 MEDLINE  
DOCUMENT NUMBER: 20173010 PubMed ID: 10709776  
TITLE: Effects of the antifungal agents on oxidative drug metabolism: clinical relevance.  
AUTHOR: Venkatakrisnan K; von Moltke L L; Greenblatt D J  
CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, Massachusetts 02111, USA.  
CONTRACT NUMBER: DA-05258 (NIDA)  
MH-19924 (NIMH)  
MH-34223 (NIMH)  
+  
SOURCE: CLINICAL PHARMACOKINETICS, (2000 Feb) 38 (2) 111-80. Ref: 539  
Journal code: DG5; 7606849. ISSN: 0312-5963.  
PUB. COUNTRY: New Zealand  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200004  
ENTRY DATE: Entered STN: 20000413  
Last Updated on STN: 20000413  
Entered Medline: 20000407

AB This article reviews the metabolic pharmacokinetic drug-drug interactions with the systemic antifungal agents: the azoles ketoconazole, miconazole, itraconazole and fluconazole, the allylamine terbinafine and the sulfonamide sulfamethoxazole. The majority of these interactions are metabolic and are caused by inhibition of cytochrome P450 (CYP)-mediated hepatic and/or small intestinal metabolism of coadministered drugs. Human liver microsomal studies in vitro, clinical case reports and controlled pharmacokinetic interaction studies in patients or healthy volunteers are reviewed. A brief overview of the CYP system and the contrasting effects of the antifungal agents on the different human drug-metabolising CYP isoforms is followed by discussion of the role of P-glycoprotein in presystemic extraction and the modulation of its function by the antifungal agents. Methods used for in vitro drug interaction studies and in vitro-in vivo scaling are then discussed, with specific emphasis on the azole antifungals. Ketoconazole and itraconazole are potent inhibitors of the major drug-metabolising CYP isoform in humans, CYP3A4. Coadministration of these drugs with CYP3A substrates such as cyclosporin, tacrolimus, alprazolam, triazolam, midazolam, nifedipine, felodipine, simvastatin, lovastatin, vincristine, terfenadine or astemizole can result in clinically significant drug interactions, some of which can be life-threatening. The interactions of ketoconazole with cyclosporin and tacrolimus have been applied for therapeutic purposes to allow a lower dosage and cost of the immunosuppressant and a reduced risk of fungal infections. The potency of fluconazole as a CYP3A4 inhibitor is much lower. Thus, clinical interactions of CYP3A substrates with this azole derivative are of lesser magnitude, and are generally observed only with fluconazole dosages of > or =200 mg/day. Fluconazole, miconazole and sulfamethoxazole are potent inhibitors of CYP2C9. Coadministration of phenytoin, warfarin, sulfamethoxazole and losartan with fluconazole results in clinically significant drug interactions. Fluconazole is a potent inhibitor of CYP2C19 in vitro, although the clinical significance of this has not been investigated. No clinically significant drug interactions have been predicted or documented between the azoles and drugs that are primarily metabolised by CYP1A2, 2D6 or 2E1. Terbinafine is a potent inhibitor of CYP2D6 and may cause clinically significant interactions with coadministered substrates of this isoform, such as nortriptyline, desipramine, perphenazine, metoprolol, encainide and propafenone. On the basis of the existing in vitro and in vivo data, drug interactions of terbinafine with substrates of other CYP isoforms are unlikely.

L8 ANSWER 18 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 96306611 MEDLINE  
DOCUMENT NUMBER: 96306611 PubMed ID: 8729584

TITLE: Development and pharmacology of fluvastatin.  
 AUTHOR: Jokubaitis L A  
 CORPORATE SOURCE: Cardiovascular Clinical Research, Sandoz Research  
 Institute, East Hanover, NJ 07936, USA.  
 SOURCE: BRITISH JOURNAL OF CLINICAL PRACTICE. SUPPLEMENT, (1996  
 Jan) 77A 11-5. Ref: 4  
 Journal code: AVL; 8007786. ISSN: 0262-8767.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199610  
 ENTRY DATE: Entered STN: 19961025  
 Last Updated on STN: 19980206  
 Entered Medline: 19961011

AB Fluvastatin is the first synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitor to be approved for clinical use, and has been studied extensively in humans since 1986. It is structurally distinct from the other currently available HMGCoA reductase inhibitors (lovastatin, simvastatin, and pravastatin), leading to unique biopharmaceutical properties relative to the other agents of this class. Absorption of fluvastatin is virtually complete across all species, including man, and is not affected by the presence of food. Systemic exposure is limited, as fluvastatin is subject to first-pass metabolism, and the plasma half-life of the drug is approximately 30 minutes. Some 95% of a single dosage of fluvastatin is excreted via the biliary route, with less than 2% of this being the parent compound. Additionally, there is no evidence of circulating active metabolites or accumulation during chronic dosing. Studies of the effect of food on the pharmacokinetics of fluvastatin have demonstrated marked reductions in the rate of bioavailability--from 40% to 60%; however, a comparison of fluvastatin administration with the evening meal or at bedtime has revealed no significant differences in the extent of bioavailability (area under the curve) of these two regimens. Furthermore, no significant difference in pharmacodynamic effect (reduction in low-density lipoprotein cholesterol levels) could be ascertained between mealtime dosing and bedtime dosing. The pharmacokinetics of fluvastatin have also been assessed in various demographic groups. Relative to the general population, plasma concentrations of fluvastatin do not vary as a function of either age or gender. In addition, administration to a patient population with hepatic insufficiency resulted in a 2.5-fold increase in both the rate and extent of bioavailability relative to controls. Also, although minimal alterations of fluvastatin clearance in patients with renal insufficiency are anticipated due to limited renal excretion (5%), a study in this patient group is currently underway to examine this further. Interaction studies have been performed with fluvastatin and several drugs with which it might be coadministered. Cholestyramine, an anionic-binding resin, has a considerable effect in lowering the rate and extent of fluvastatin bioavailability. Although this effect was noted even when cholestyramine was given 4 hours prior to fluvastatin, this regimen did not result in diminished efficacy. Further, no effects on either warfarin levels or prothrombin times were observed in a study involving concomitant administration of warfarin and fluvastatin. Moreover, additional interaction studies with niacin and propranolol have not demonstrated any effect on fluvastatin plasma levels, and administration to a patient population chronically receiving digoxin resulted in no difference in the extent of bioavailability of digoxin relative to control data. The results generated to date in clinical pharmacokinetic studies with fluvastatin thus support its use in a broad population of hypercholesterolaemic patients.

L8 ANSWER 19 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS

Full-text

ACCESSION NUMBER: 1992:436123 BIOSIS  
 DOCUMENT NUMBER: BA94:88248  
 TITLE: PRIMARY AND SECONDARY PREVENTION OF CORONARY ARTERY  
 DISEASE.  
 AUTHOR(S): GOTTO A M JR  
 CORPORATE SOURCE: DEP. MED., MS SM-1423, BAYLOR COLL. MED., 6550 FANNIN,  
 HOUSTON, TEXAS 77030.  
 SOURCE: CURR OPIN CARDIOL, (1992) 7 (4), 553-562.  
 CODEN: COPCE3.  
 FILE SEGMENT: BA; OLD  
 LANGUAGE: English

AB A variety of new results from clinical studies point toward improved assessment of and intervention in risk factors for coronary artery disease. Separate analyses of Helsinki Heart Study and Prospective Cardiovascular Muenster (PROCAM) data showed the combination of triglyceride elevation and a high ratio of total cholesterol or low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) to confer greater risk of coronary artery disease than LDL-C elevation alone. In the Physicians' Health Study (PHS), a change of 1 unit in the total to HDL cholesterol ratio was associated with a 53% change in risk for myocardial infarction after adjustment for other risk factors. Findings from these studies support recommendations by the February 1992 US National Institutes of Health Consensus Development Conference on Triglyceride, High Density Lipoprotein, and Coronary Heart Disease that not only total cholesterol but also HDL-C be measured in healthy individuals to assess coronary artery disease risk and that HDL-C and triglyceride be measured in additional clinical circumstances, eg, in patients with known coronary artery disease or with desirable total cholesterol and two or more risk factors and in such disorders as hypertension and diabetes mellitus, to refine risk assessment. Strong evidence associates much-increased coronary artery disease risk with atherogenic lipoprotein phenotype B, in which presumably atherogenic small, dense LDL particles predominate. A meta-analysis of major cholesterol-lowering trials suggested that targeted secondary intervention could have a major impact on coronary artery disease events in the entire population, because there were 27 fewer myocardial infarctions than expected per 1000 patients treated across eight secondary-intervention trials, compared with six per 1000 across four primary-prevention trials, and because half of all myocardial infarctions occur in men with a history of coronary artery disease. Noteworthy new results have also been published on nonlipid variables in relation to coronary artery disease risk, including aspirin use, propranolol use, tissue plasminogen activator antigen level, family history of myocardial infarction, and adipose distribution. There are promising new findings that directing educational programs on lifestyle risk factors toward families or communities can be effective. The approval in 1991 of two additional reductase inhibitors (pravastatin and simvastatin) for use in the United States provides options in a class of drugs with excellent efficacy and safety records, recently bolstered by publication of the findings of the Expanded Clinical Evaluation of Lovastatin (EXCEL) study.

IT Miscellaneous Descriptors

REVIEW HUMAN LOVASTATIN PRAVASTATIN SIMVASTATIN ENZYME  
INHIBITOR-DRUG ASPIRIN PROPRANOLOL NITRATE ANTIATHEROGENIC-DRUG  
TISSUE PLASMINOGEN ACTIVATOR THROMBOLYTIC-DRUG HIGH DENSITY LIPOPROTEIN  
CHOLESTEROL LOW DENSITY LIPOPROTEIN CHOLESTEROL MYOCARDIAL INFARCTION  
HYPERTENSION DIABETES MELLITUS

L8 ANSWER 20 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 2000495716 MEDLINE  
DOCUMENT NUMBER: 20398558 PubMed ID: 10940116  
TITLE: Infiltrating basal cell carcinoma in the setting of a venous ulcer.  
AUTHOR: Lutz M E; Davis M D; Otley C C  
CORPORATE SOURCE: Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.  
SOURCE: INTERNATIONAL JOURNAL OF DERMATOLOGY, (2000 Jul) 39 (7) 519-20.  
Journal code: GR2; 0243704. ISSN: 0011-9059.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200010  
ENTRY DATE: Entered STN: 20001027  
Last Updated on STN: 20001027  
Entered Medline: 20001018

AB A 77-year-old man was referred with a 5-year history of an intermittently painful, nonhealing right medial ankle ulcer. The ulcer had not responded to multiple treatment modalities, including Unna boots, compression therapy, sclerotherapy, and split-thickness skin grafting. The past medical history was significant for a deep venous thrombosis in the right leg 30 years earlier (treated with warfarin for 3 months) and a history of greater saphenous vein harvesting for coronary bypass grafting 28 years previously. After the vein stripping, the patient had suffered from increasing right leg edema and stasis changes in the right leg. His

history was also remarkable for coronary artery disease, dyslipidemia, and lymphoma treated with chemotherapy 8 years before presentation, with no evidence of recurrence. He had stopped smoking approximately 20 years earlier. Medications included atenolol, simvastatin, nicardipine, nitroglycerin, and aspirin. Skin examination revealed a 3.0 x 3.5-cm ulcer adjacent to the medial malleolus. The edges of the ulcer appeared raised and rolled (Fig. 1). Centrally, there was granulation tissue, which appeared healthy. There were surrounding dermatitic changes. Dorsalis pedis and the posterior tibial pulses were normal. Noninvasive vascular studies revealed severe venous incompetence of the right popliteal and superficial veins. Arterial studies and transcutaneous oximetry were normal. Computed tomographic scan of the pelvis did not reveal any adenopathy, and radiographic imaging did not reveal any bony changes suggestive of osteomyelitis. Biopsy of the ulcer edge and base showed infiltrating basal cell carcinoma (Fig. 2). Mohs' micrographic surgery required three layers; the final extent of the ulcer was 7.8 x 6.9 cm. A split-thickness skin graft was placed.

=> d ti tot

- L8 ANSWER 1 OF 96 MEDLINE
- TI Pharmacokinetic interaction between propranolol and the HMG-CoA reductase inhibitors pravastatin and lovastatin.
  
- L8 ANSWER 2 OF 96 MEDLINE
- TI Simvastatin inhibits noradrenaline-induced hypertrophy of cultured neonatal rat cardiomyocytes.
  
- L8 ANSWER 3 OF 96 MEDLINE
- TI [Severe rhabdomyolysis in a patient receiving lovastatin, danazol, and doxycycline].  
Rhabdomyolyse severe chez un patient recevant lovastatine, danazol et doxycycline.
  
- L8 ANSWER 4 OF 96 USPATFULL
- TI In vivo delivery methods and compositions
  
- L8 ANSWER 5 OF 96 MEDLINE
- TI Clinical implications of the biopharmaceutical properties of fluvastatin.
  
- L8 ANSWER 6 OF 96 CAPLUS COPYRIGHT 2001 ACS
- TI Formulation for the prevention of cardiovascular disease
  
- L8 ANSWER 7 OF 96 USPATFULL
- TI Biodegradable polymers chain-extended by phosphates, compositions, articles and methods for making and using the same
  
- L8 ANSWER 8 OF 96 MEDLINE
- TI Nightmares and sleep disturbances with simvastatin and metoprolol.
  
- L8 ANSWER 9 OF 96 MEDLINE
- TI In the past 12 to 18 months, my level of anxiety has increased significantly. I have been on atenolol and simvastatin (Zocor) for the past couple of years. Is there anything in these drugs that could cause this anxiety?.
  
- L8 ANSWER 10 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS
- TI Nightmares and sleep disturbances with simvastatin and metoprolol.
  
- L8 ANSWER 11 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS
- TI Effects of hypolipemic therapy on the pharmacokinetics of propranolol.
  
- L8 ANSWER 12 OF 96 USPATFULL
- TI Biodegradable terephthalate polyester-poly (phosphate) polymers, compositions, articles, and methods for making and using the same
  
- L8 ANSWER 13 OF 96 USPATFULL
- TI Biodegradable terephthalate polyester-poly (phosphonate) compositions, articles, and methods of using the same
  
- L8 ANSWER 14 OF 96 USPATFULL
- TI Two-stage solution polymerization of high molecular weight poly(phosphoesters)
  
- L8 ANSWER 15 OF 96 USPATFULL

TI Solution polymerization of high molecular weight poly(phosphoesters) in toluene

L8 ANSWER 16 OF 96 USPATFULL  
TI Biodegradable controlled release flash flow melt-spun delivery system

L8 ANSWER 17 OF 96 MEDLINE  
TI Effects of the antifungal agents on oxidative drug metabolism: clinical relevance.

L8 ANSWER 18 OF 96 MEDLINE  
TI Development and pharmacology of fluvastatin.

L8 ANSWER 19 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS  
TI PRIMARY AND SECONDARY PREVENTION OF CORONARY ARTERY DISEASE.

L8 ANSWER 20 OF 96 MEDLINE  
TI Infiltrating basal cell carcinoma in the setting of a venous ulcer.

L8 ANSWER 21 OF 96 MEDLINE  
TI Failure of educational videotapes to improve medication compliance in a health maintenance organization.

L8 ANSWER 22 OF 96 MEDLINE  
TI Cataracts in systemic diseases and syndromes.

L8 ANSWER 23 OF 96 MEDLINE  
TI Secondary prevention for ischemic heart disease. Relative numbers needed to treat with different therapies.

L8 ANSWER 24 OF 96 USPATFULL  
TI Clear oil-containing pharmaceutical compositions

L8 ANSWER 25 OF 96 USPATFULL  
TI Bioadhesive progressive hydration tablets and methods of making and using the same

L8 ANSWER 26 OF 96 USPATFULL  
TI Method for preventing or reducing photosensitivity and or phototoxicity reaction to medications

L8 ANSWER 27 OF 96 USPATFULL  
TI Stereospecific delivery of a drug using electrotransport

L8 ANSWER 28 OF 96 USPATFULL  
TI Medicinal and/or nutritional microcapsules for oral administration

L8 ANSWER 29 OF 96 USPATFULL  
TI Method for preventing or reducing photosensitivity and/or phototoxicity reactions to medications

L8 ANSWER 30 OF 96 MEDLINE  
TI Care of adults with type 2 diabetes mellitus. A review of the evidence.

L8 ANSWER 31 OF 96 USPATFULL  
TI Solid dosage form with polymeric binder

L8 ANSWER 32 OF 96 USPATFULL  
TI TREATING OR PREVENTING THE EARLY STAGES OF DEGENERATION OF ARTICULAR CARTILAGE OR SUBCHONDRAL BONE IN MAMMALS USING CARPROFEN AND DERIVATIVES

L8 ANSWER 33 OF 96 USPATFULL  
TI Process for producing solid dosage forms by extrusion

L8 ANSWER 34 OF 96 USPATFULL  
TI Solid medicaments obtained by extrusion of an isomalt-containing polymer-active substance melt

L8 ANSWER 35 OF 96 USPATFULL  
TI Solid foamed active substance preparations

L8 ANSWER 36 OF 96 USPATFULL  
TI Production of lenticular tablets by melt calendering

L8 ANSWER 37 OF 96 USPATFULL

TI Method of producing multi-layer medicaments in solid form for oral or rectal administration

L8 ANSWER 38 OF 96 USPATFULL  
TI Production of solid drug forms

L8 ANSWER 39 OF 96 USPATFULL  
TI Process and apparatus for the production of divisible tablets

L8 ANSWER 40 OF 96 USPATFULL  
TI Process for producing solid drug forms having at least two phases

L8 ANSWER 41 OF 96 USPATFULL  
TI Solid active extrusion compound preparations containing low-substituted hydroxypropylcellulose

L8 ANSWER 42 OF 96 USPATFULL  
TI Production of covered tablets

L8 ANSWER 43 OF 96 USPATFULL  
TI Controlled release simvastatin delivery device

L8 ANSWER 44 OF 96 USPATFULL  
TI Controlled release drug suspension delivery device

L8 ANSWER 45 OF 96 USPATFULL  
TI Controlled release nifedipine delivery device

L8 ANSWER 46 OF 96 USPATFULL  
TI Controlled release drug dispersion delivery device

L8 ANSWER 47 OF 96 USPATFULL  
TI Spheronization process using charged resins

L8 ANSWER 48 OF 96 USPATFULL  
TI Process for producing a tablet core aperture

L8 ANSWER 49 OF 96 USPATFULL  
TI Dosage form for delivering a drug at two different rates

L8 ANSWER 50 OF 96 MEDLINE  
TI The impact of specialists on prescribing by general practitioners.

L8 ANSWER 51 OF 96 MEDLINE  
TI [An overview of hypertension studies with calcium antagonists].  
Oversikt over hypertensjonsstudier med kalsiumantagonister. ASCOT.  
Anglo-Scandinavian Cardiac Outcomes Trial.

L8 ANSWER 52 OF 96 CAPLUS COPYRIGHT 2001 ACS  
TI A case with renovascular hypertension

L8 ANSWER 53 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS  
TI Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian cardiac outcomes trial.

L8 ANSWER 54 OF 96 USPATFULL  
TI New compounds, their preparation and use

L8 ANSWER 55 OF 96 USPATFULL  
TI Bioadhesive solid dosage form

L8 ANSWER 56 OF 96 USPATFULL  
TI Conjugates of dithiocarbamate disulfides with pharmacologically active agents and uses therefor

L8 ANSWER 57 OF 96 USPATFULL  
TI Anti-first-pass effect compounds

L8 ANSWER 58 OF 96 USPATFULL  
TI Fatty acid-pharmaceutical agent conjugates

L8 ANSWER 59 OF 96 USPATFULL  
TI Pharmaceutical compositions in semisolid form and a device for administration thereof

L8 ANSWER 60 OF 96 USPATFULL  
 TI Spill resistant pharmaceutical compositions in semi-solid form

L8 ANSWER 61 OF 96 USPATFULL  
 TI Purified galactomannan as an improved pharmaceutical excipient

L8 ANSWER 62 OF 96 USPATFULL  
 TI Conjugates of dithiocarbamates with pharmacologically active agents and uses therefore

L8 ANSWER 63 OF 96 USPATFULL  
 TI Medicinal adjuvants consisting of N-substituted-o-toluidine derivatives, and percutaneously absorbable preparations comprising the adjuvants

L8 ANSWER 64 OF 96 USPATFULL  
 TI Pharmaceutical compositions in semisolid form and a device for administration thereof

L8 ANSWER 65 OF 96 USPATFULL  
 TI Transdermal delivery of medications using a combination of penetration enhancers

L8 ANSWER 66 OF 96 USPATFULL  
 TI DHA-pharmaceutical agent conjugates of taxanes

L8 ANSWER 67 OF 96 USPATFULL  
 TI Method of detecting cytopenia that is mediated by drug-dependent antibody binding to blood cells

L8 ANSWER 68 OF 96 USPATFULL  
 TI Composition and method for treating diabetes

L8 ANSWER 69 OF 96 USPATFULL  
 TI Method of using deuterated calcium channel blockers

L8 ANSWER 70 OF 96 USPATFULL  
 TI Methods and compositions for the rapid and enduring relief of inadequate myocardial function

L8 ANSWER 71 OF 96 USPATFULL  
 TI Use of nebivolol as an anti-atherogenic

L8 ANSWER 72 OF 96 USPATFULL  
 TI Use of Nebivolol as an anti-atherogenic

L8 ANSWER 73 OF 96 USPATFULL  
 TI Methods and compositions for the rapid and enduring relief of inadequate myocardial function

L8 ANSWER 74 OF 96 USPATFULL  
 TI Enhancement of the efficacy of nifedipine by deuteration

L8 ANSWER 75 OF 96 USPATFULL  
 TI Once daily pharmaceutical tablet having a unitary core

L8 ANSWER 76 OF 96 USPATFULL  
 TI Method for controlling and/or lowering serum glucose and fatty acid concentrations and hypertensive blood pressure in non-insulin-dependent diabetic patients

L8 ANSWER 77 OF 96 USPATFULL  
 TI Diffusion-osmotic controlled drug-release pharmaceutical composition and process for preparing same

L8 ANSWER 78 OF 96 USPATFULL  
 TI Uncoated tablets and method of producing the same

L8 ANSWER 79 OF 96 BIOSIS COPYRIGHT 2001 BIOSIS  
 TI LONG-TERM TREATMENT FOLLOWING ACUTE MYOCARDIAL INFARCTION.

L8 ANSWER 80 OF 96 USPATFULL  
 TI Arrays of nucleic acid probes for analyzing biotransformation genes and methods of using the same



L8 ANSWER 81 OF 96 USPATFULL  
 TI Sachet formulations

L8 ANSWER 82 OF 96 USPATFULL  
 TI Embedding and encapsulation of controlled release particles

L8 ANSWER 83 OF 96 USPATFULL  
 TI Dosage forms containing taste masked active agents

L8 ANSWER 84 OF 96 USPATFULL  
 TI Fatty ester combinations

L8 ANSWER 85 OF 96 USPATFULL  
 TI Method for treating respiratory distress by sublingual administration of DNA

L8 ANSWER 86 OF 96 USPATFULL  
 TI Method for treating mucositis by sublingual administration of DNA

L8 ANSWER 87 OF 96 USPATFULL  
 TI Disintegratable microspheres

L8 ANSWER 88 OF 96 USPATFULL  
 TI Fast-dissolving comestible units formed under high-speed/high-pressure conditions

L8 ANSWER 89 OF 96 USPATFULL  
 TI Immediate release dosage forms containing microspheres

L8 ANSWER 90 OF 96 USPATFULL  
 TI Self-binding shearform compositions

L8 ANSWER 91 OF 96 USPATFULL  
 TI Method of treating colonic adenomas

L8 ANSWER 92 OF 96 USPATFULL  
 TI Treatment of otitis media by sublingual administration of DNA

L8 ANSWER 93 OF 96 USPATFULL  
 TI Fast-dissolving comestible units formed under high-speed/high-pressure conditions

L8 ANSWER 94 OF 96 USPATFULL  
 TI Self-binding shearform compositions

L8 ANSWER 95 OF 96 USPATFULL  
 TI Antibiotic oil suspensions

L8 ANSWER 96 OF 96 USPATFULL  
 TI Nasally administrable compositions

=> d ibib abs kwic 21-23

L8 ANSWER 21 OF 96 MEDLINE  
Full-text  
 ACCESSION NUMBER: 96119408 MEDLINE  
 DOCUMENT NUMBER: 96119408 PubMed ID: 8564589  
 TITLE: Failure of educational videotapes to improve medication compliance in a health maintenance organization.  
 AUTHOR: Powell K M; Edgren B  
 CORPORATE SOURCE: Diversified Pharmaceutical Services, Minneapolis, MN 55440-9422, USA.  
 SOURCE: AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (1995 Oct 15) 52 (20) 2196-9.  
 Journal code: CBH; 9503023. ISSN: 1079-2082.  
 PUB. COUNTRY: United States  
 (CLINICAL TRIAL)  
 Journal; Article; (JOURNAL ARTICLE)  
 (RANDOMIZED CONTROLLED TRIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199603  
 ENTRY DATE: Entered STN: 19960315  
 Last Updated on STN: 19960315

Entered Medline: 19960306

AB The value of mailed educational videotapes as a means of enhancing compliance with drug therapy was studied. Members of a health maintenance organization with a pharmacy claim for benazepril, metoprolol, simvastatin, or transdermal estrogen were randomly assigned to a study group or a control group. Subjects in the study group were mailed one of four videotape programs giving information on the drug prescribed and the inferred disease state. Control subjects received no educational materials. Subjects were enrolled from July 1, 1993, through January 2, 1994. Refill data were collected from July 1, 1993, through April 1, 1994. The medication possession ratio (MPR) was calculated as the total number of days' supply of a drug obtained by a member divided by the number of days between the time of enrollment and April 1, 1994, or the date the member was terminated from the plan. A subject was deemed compliant if his or her MPR was  $\geq 0.80$ . There were no significant differences in mean MPRs between the study group (n = 1993) and the control group (n = 2253). None of the mean MPRs was  $\geq 0.80$ , although 44% of control subjects and 46% of study-group subjects were compliant. Of 97 respondents to a survey mailed to a randomly selected subset of the study group, almost 87% reported that they had viewed the videotapes, and of these subjects, about 88% said they found them very useful or somewhat useful. A one-time mailing of videotapes to patients, with no individual follow-up, did not increase compliance with the medications monitored.

L8 ANSWER 22 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 95399905 MEDLINE  
DOCUMENT NUMBER: 95399905 PubMed ID: 10150840  
TITLE: Cataracts in systemic diseases and syndromes.  
AUTHOR: Bariciak M D; Nichols B D  
CORPORATE SOURCE: University of Western Ontario, London, Canada.  
SOURCE: CURRENT OPINION IN OPHTHALMOLOGY, (1995 Feb) 6 (1) 3-8.  
Ref: 32  
Journal code: BB4; 9011108. ISSN: 1040-8738.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: T  
ENTRY MONTH: 199510  
ENTRY DATE: Entered STN: 20010223  
Last Updated on STN: 20010223  
Entered Medline: 19951013

AB A comprehensive review of the ophthalmic literature on cataracts during the past year is presented. Topics covered include new epidemiologic associations, diabetic cataracts, and syndromes involving cataracts. Data from the Beaver Dam Eye Study suggest the presence of a recessive gene for nuclear sclerosis. Estrogen exposure may decrease the risk of nuclear sclerosis. The effects of amiodarone, propranolol, and lovastatin on the lens are discussed. Electron microscopy studies have furthered our understanding of diabetic cataracts and the rare Christmas tree cataract. Two new studies support the adverse effect of extracapsular cataract extraction on diabetic retinopathy. New associations between neurofibromatosis 2 and the lens will aid in the diagnosis of this condition. Other ocular and systemic syndromes are discussed.

AB . . . of a recessive gene for nuclear sclerosis. Estrogen exposure may decrease the risk of nuclear sclerosis. The effects of amiodarone, propranolol, and lovastatin on the lens are discussed. Electron microscopy studies have furthered our understanding of diabetic cataracts and the rare Christmas tree. . . .

L8 ANSWER 23 OF 96 MEDLINE

Full-text

ACCESSION NUMBER: 1998022096 MEDLINE  
DOCUMENT NUMBER: 98022096 PubMed ID: 9382659  
TITLE: Secondary prevention for ischemic heart disease. Relative numbers needed to treat with different therapies.  
AUTHOR: Miller D B  
CORPORATE SOURCE: Department of Medicine, University of Western Ontario, London.. dmiller@ampsc.com  
SOURCE: ARCHIVES OF INTERNAL MEDICINE, (1997 Oct 13) 157 (18) 2045-52. Ref: 38  
Journal code: 7FS; 0372440. ISSN: 0003-9926.  
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 199711  
ENTRY DATE: Entered STN: 19971224  
Last Updated on STN: 19971224  
Entered Medline: 19971110

- AB Secondary prevention of ischemic heart disease refers to the process of preventing further morbidity and reducing mortality rates in patients with clinical manifestations of the disease. Twenty-five large randomized, clinical trials addressing mortality rates and cardiovascular morbidity in patients with established ischemic heart disease are reviewed. Broadly defined, these were trials of aspirin and antiplatelet agents, anticoagulants, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, lowering of cholesterol levels, exercise rehabilitation, and diet or vitamins. In trials using warfarin sodium, timolol maleate, propranolol hydrochloride, captopril, ramipril, and simvastatin and 2 diet studies, statistically significant improvements in total mortality rates were seen. Most other studies showed non-significant reductions in total mortality rates, with statistically significant reductions in 1 or more measures of cardiovascular morbidity. The methods necessary for the reader to calculate the number (of patients) needed to treat for other studies are also reviewed. The uses and limitations of the number needed to treat as a method to compare studies of different interventions in similar populations are discussed.
- AB . . . . angiotensin-converting enzyme inhibitors, lowering of cholesterol levels, exercise rehabilitation, and diet or vitamins. In trials using warfarin sodium, timolol maleate, propranolol hydrochloride, captopril, ramipril, and simvastatin and 2 diet studies, statistically significant improvements in total mortality rates were seen. Most other studies showed non-significant reductions in. . .

=> index bioscience

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	70.84	109.00

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-0.59	-0.59

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCERAMICS, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'

ENTERED AT 10:40:50 ON 04 DEC 2001

59 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view search error messages that display as 0\* with SET DETAIL OFF.

=> s lovastatin or simvastatin or atorvastatin or cerivastatin

3561	FILE ADISALERTS
37	FILE ADISINSIGHT
695*	FILE ADISNEWS
76	FILE AGRICOLA
44	FILE ANABSTR
2	FILE AQUASCI
254	FILE BIOBUSINESS
11	FILE BIOCERAMICS
4318	FILE BIOSIS
64	FILE BIOTECHABS
64	FILE BIOTECHDS
619	FILE BIOTECHNO
195	FILE CABA
517	FILE CANCERLIT
2720	FILE CAPLUS
26	FILE CEABA-VTB
16	FILE CEN
237	FILE CIN

268 FILE CONFSCI  
 20 FILES SEARCHED...  
 4 FILE CROPU  
 4468 FILE DDFU  
 75 FILE DGENE  
 556 FILE DRUGLAUNCH  
 586 FILE DRUGMONOG2  
 82 FILE DRUGNL  
 4545 FILE DRUGU  
 32 FILE DRUGUPDATES  
 88 FILE EMBAL

31 FILES SEARCHED...  
 6385 FILE EMBASE  
 1145 FILE ESBIODBASE  
 30 FILE FROSTI  
 12 FILE FSTA  
 22 FILE GENBANK  
 7 FILE HEALSAFE  
 155 FILE IFIPAT  
 283 FILE JICST-EPLUS  
 4 FILE KOSMET  
 269 FILE LIFESCI  
 4116 FILE MEDLINE  
 6 FILE NTIS

47 FILES SEARCHED...  
 1874 FILE PASCAL  
 34 FILE PHAR  
 19 FILE PHIC  
 1137 FILE PHIN  
 1285 FILE PROMT  
 4667 FILE SCISEARCH  
 4 FILE SYNTHLINE  
 1666 FILE TOXLIT  
 1091 FILE USPATFULL  
 285 FILE WPIDS  
 285 FILE WPINDEX

51 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L9 QUE LOVASTATIN OR SIMVASTATIN OR ATORVASTATIN OR CERIVASTATIN

=> s propranolol or atenolol or metoprolol

5752 FILE ADISALERTS  
 124 FILE ADISINSIGHT  
 1237\* FILE ADISNEWS  
 214 FILE AGRICOLA  
 848 FILE ANABSTR  
 158 FILE AQUASCI  
 669 FILE BIOBUSINESS  
 5 FILE BIOCOMMERCE  
 43720 FILE BIOSIS  
 42 FILE BIOTECHABS  
 42 FILE BIOTECHDS  
 3069 FILE BIOTECHNO  
 1130 FILE CABA  
 1106 FILE CANCERLIT  
 28491 FILE CAPLUS

15 FILES SEARCHED...  
 10 FILE CEABA-VTB  
 11 FILE CEN  
 169 FILE CIN  
 1081 FILE CONFSCI  
 8 FILE CROPB  
 30 FILE CROPU  
 23131 FILE DDFB  
 32980 FILE DDFU  
 8 FILE DGENE  
 23131 FILE DRUGB  
 1338 FILE DRUGLAUNCH  
 2645 FILE DRUGMONOG2  
 22 FILE DRUGNL  
 34352 FILE DRUGU  
 70 FILE DRUGUPDATES  
 94 FILE EMBAL  
 76316 FILE EMBASE

```

3160 FILE ESBIODBASE
35 FILES SEARCHED...
10 FILE FROSTI
10 FILE FSTA
1 FILE GENBANK
53 FILE HEALSAFE
367 FILE IFIPAT
1611 FILE JICST-EPLUS
13 FILE KOSMET
2802 FILE LIFESCI
41706 FILE MEDLINE
234 FILE NIOSHTIC
120 FILE NTIS
33 FILE OCEAN
8324 FILE PASCAL
135 FILE PHAR
4 FILE PHIC
1603 FILE PHIN
924 FILE PROMT

```

```

53 FILES SEARCHED...
21532 FILE SCISEARCH
1 FILE SYNTHLINE
22065 FILE TOXLIT
3466 FILE USPATFULL
476 FILE WPIDS
476 FILE WPINDEX

```

56 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L10 QUE PROPRANOLOL OR ATENOLOL OR METOPROLOL

=> s 19 and 110

```

74 FILE ADISALERTS
2 FILE ADISINSIGHT
32* FILE ADISNEWS
2 FILE ANABSTR
1 FILE BIOBUSINESS
14 FILE BIOSIS
11 FILES SEARCHED...
18 FILE BIOTECHNO
2 FILE CANCERLIT
48 FILE CAPLUS
1 FILE CEN
22 FILES SEARCHED...
204 FILE DDFU
1 FILE DRUGNL
223 FILE DRUGU
29 FILES SEARCHED...
1 FILE DRUGUPDATES
3 FILE EMBAL
268 FILE EMBASE
4 FILE ESBIODBASE
8 FILE IFIPAT
1 FILE JICST-EPLUS
1 FILE LIFESCI

```

```

44 FILES SEARCHED...
19 FILE MEDLINE
6 FILE PASCAL
51 FILE PHIN
31 FILE PROMT
19 FILE SCISEARCH
8 FILE TOXLIT

```

```

56 FILES SEARCHED...
129 FILE USPATFULL
14 FILE WPIDS
14 FILE WPINDEX

```

29 FILES HAVE ONE OR MORE ANSWERS, 59 FILES SEARCHED IN STNINDEX

L11 QUE L9 AND L10

=> d rank

```

F1 268 EMBASE
F2 223 DRUGU
F3 204 DDFU

```

F4	129	USPATFULL
F5	74	ADISALERTS
F6	51	PHIN
F7	48	CAPLUS
F8	32*	ADISNEWS
F9	31	PROMT
F10	19	MEDLINE
F11	19	SCISEARCH
F12	18	BIOTECHNO
F13	14	BIOSIS
F14	14	WPIDS
F15	14	WPINDEX
F16	8	IFIPAT
F17	8	TOXLIT
F18	6	PASCAL
F19	4	ESBIOBASE
F20	3	EMBAL
F21	2	ADISINSIGHT
F22	2	ANABSTR
F23	2	CANCERLIT
F24	1	BIOBUSINESS
F25	1	CEN
F26	1	DRUGNL
F27	1	DRUGUPDATES
F28	1	JICST-EPLUS
F29	1	LIFESCI

=> fil f1-3 f5 f8-11 f14-15

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.18	118.18

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.59

FILE 'EMBASE' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 Elsevier Science B.V. All rights reserved.

FILE 'DRUGU' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'DDFU' ACCESS NOT AUTHORIZED

FILE 'ADISALERTS' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 Adis International Ltd. (ADIS)

FILE 'ADISNEWS' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 Adis International Ltd. (ADIS)

FILE 'PROMT' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 Gale Group. All rights reserved.

FILE 'MEDLINE' ENTERED AT 10:51:27 ON 04 DEC 2001

FILE 'SCISEARCH' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 Institute for Scientific Information (ISI) (R)

FILE 'WPIDS' ENTERED AT 10:51:27 ON 04 DEC 2001  
 COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'WPINDEX' ACCESS NOT AUTHORIZED

=> s l11  
 7 FILES SEARCHED...  
 L12 680 L11

=> dup rem l12  
 DUPLICATE IS NOT AVAILABLE IN 'ADISNEWS'.  
 ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE  
 PROCESSING IS APPROXIMATELY 97% COMPLETE FOR L12  
 PROCESSING COMPLETED FOR L12  
 L13 592 DUP REM L12 (88 DUPLICATES REMOVED)

=> s cardio? and l13  
L14 192 CARDIO? AND L13

=> focus  
PROCESSING COMPLETED FOR L14  
L15 192 FOCUS L14 1-

=> d ibib abs kwic 1-5

L15 ANSWER 1 OF 192 PROMT COPYRIGHT 2001 Gale Group  
Full-text

ACCESSION NUMBER: 1998:588061 PROMT  
TITLE: Follow-Up Data From Landmark Cholesterol Study Indicate  
Life-Saving Benefits of Zocor(R) Are Maintained.  
SOURCE: PR Newswire, (11 Nov 1998) pp. 0631.  
LANGUAGE: English  
WORD COUNT: 8273

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB DALLAS, Nov. 11 /PRNewswire/ -- Follow-up data from the landmark Scandinavian Simvastatin Survival Study (4S) with the Merck & Co., Inc. (NYSE: MRK), cholesterol-lowering drug Zocor(R) (simvastatin) have shown that the 30 percent reduction in risk of death observed in the original 5-year study has been maintained during extended 2-year follow-up study, with survival benefits now being reported for a median 7.4 years, and in some patients for up to 8 years. The data were presented at the 71st Scientific Sessions of the American Heart Association (AHA).

"An important measure of the long-term efficacy and safety profile of a cholesterol-lowering medicine is its impact on mortality," said Terje Pedersen, M.D., professor of clinical cardiology at Aker University Hospital in Oslo, Norway, and principal investigator for 4S. "These follow-up data are exciting because they indicate that the life-saving benefits of long-term therapy with Zocor seen at the end of the original 5.4-year trial in patients with high cholesterol and coronary heart disease were maintained for an additional two years following the study conclusion."

#### Recommended Use of Zocor

In patients with coronary heart disease (CHD) and high cholesterol, Zocor is indicated to reduce the risk of total mortality, non-fatal myocardial infarction, myocardial revascularization procedures, and stroke or transient ischemic attack. Zocor should be used in addition to diet to lower elevated cholesterol levels after diet alone has failed to achieve target levels. In patients who have been hospitalized with an acute coronary event, such as a heart attack or worsening chest pain, consideration can be given to initiating drug therapy at the time of discharge if LDL cholesterol levels are at 130 mg/dL or higher.

THIS IS AN EXCERPT: COPYRIGHT 1998 PR Newswire Association, Inc.

DALLAS, Nov. 11 /PRNewswire/ -- Follow-up data from the landmark Scandinavian Simvastatin Survival Study (4S) with the Merck & Co., Inc. (NYSE: MRK), cholesterol-lowering drug Zocor(R) (simvastatin) have shown that the 30 percent reduction in risk of death observed in the original 5-year study has been maintained.

"An . . . efficacy and safety profile of a cholesterol-lowering medicine is its impact on mortality," said Terje Pedersen, M.D., professor of clinical cardiology at Aker University Hospital in Oslo, Norway, and principal investigator for 4S. "These follow-up data are exciting because they indicate. . .

TX DALLAS, Nov. 11 /PRNewswire/ -- Follow-up data from the landmark Scandinavian Simvastatin Survival Study (4S) with the Merck & Co., Inc. (NYSE: MRK), cholesterol-lowering drug Zocor(R) (simvastatin) have shown that the 30 percent reduction in risk of death observed in the original 5-year study has been maintained.

"An . . . efficacy and safety profile of a cholesterol-lowering medicine is its impact on mortality," said Terje Pedersen, M.D., professor of clinical cardiology at Aker University Hospital in Oslo, Norway, and principal investigator for 4S. "These follow-up data are exciting because they indicate. . .

Deaths from both cardiovascular and non-cardiovascular causes were examined in the analysis of health records. Of the patients who had been treated with Zocor, approximately 2.3. . .

For other cardiovascular and non-cardiovascular deaths, the numbers were similar for the two groups.

Of . . . The response rate to the survey was 88.4 percent for the original placebo group and 89.4 percent for the original simvastatin

group. 4S: Driving Treatment Evolution

"The . . . disease," said Sidney C. Smith, Jr., M.D., former president of the AHA and professor and chief of the division of cardiology at the University of North Carolina at Chapel Hill. "Many people have benefited throughout the world because of what physicians. . .

(SIMVASTATIN)

ZOCOR\* (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A. . .

Simvastatin is butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1alpha,3alpha,7beta,8beta (2S\*,4S\*)]-8 alpha beta]]. The empirical formula of simvastatin is C<sub>25</sub>H<sub>38</sub>O<sub>5</sub> and its molecular weight is 418.57. Its structural formula is:

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol. . .

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and.

The . . . for coronary heart disease (CHD). The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4,444 patients with. . .

Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition. . . the beta-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of 14C-labeled simvastatin in man, 13 percent of the dose was excreted in urine and 60 percent in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus 14C-metabolites) peaked at 4 hours and declined rapidly to about 10 percent of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85 percent of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be greater than 60 percent in man), the availability of drug to the general circulation is low. In. . . a single-dose study in nine healthy subjects, it was estimated that less than 5 percent of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48 percent for the area under the concentration-time curve. . .

Both simvastatin and its beta-hydroxyacid metabolite are highly bound (approximately 95 percent) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the beta-hydroxyacid of simvastatin and its 6c-hydroxy, 6c-hydroxymethyl, and 6c-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3. . . to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

The results of 3 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia are presented in TABLE 1.

In a controlled clinical study, 12 patients 15-39 years of age with



homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of . . .

In . . . significantly reduced by 42 percent, ( $p$  equals 0.00001, 111 vs 189). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial . . .

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, . . . (6.4 mmol/L) and a mean baseline LDL-C value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a . . . endpoints of the trial were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the final angiogram by both these parameters (mean changes in minimum lumen diameter: 0.04 mm with simvastatin vs 0.12 mm with placebo; mean changes in mean lumen diameter: 0.03 mm with simvastatin vs 0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9 percent simvastatin vs 3.6 percent placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23 percent simvastatin vs 33 percent placebo) and disease regression (18 percent simvastatin vs 12 percent placebo). In addition, simvastatin significantly decreased the proportion of patients with new lesions (13 percent simvastatin vs 24 percent placebo) and with new total occlusions (5 percent vs 11 percent). The mean change per-patient in . . .

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin (hCG). In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg or placebo daily for a median duration of 5.4 years, the incidence of male sexual adverse events in . . .

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism). . . .

Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly . . . failure secondary to myoglobinuria, has been reported rarely. In 4S, there was one case of myopathy among 1,399 patients taking simvastatin 20 mg and no cases among 822 patients taking 40 mg daily for a median duration of 5.4 years. In . . .

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin. . . .

1. General measures. Patients starting therapy with simvastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A CK level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, . . .

Of . . . patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. . . . reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, Drug Interactions). Physicians contemplating combined therapy with simvastatin and any of the interacting drugs

should weigh the potential benefits and risks, and should carefully monitor patients for any. . .

The combined use of **simvastatin** with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of **simvastatin** have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to **simvastatin** typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. . . .

one of these drugs must be used with **simvastatin**, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of **simvastatin** should generally not exceed 10 mg (see DOSAGE AND ADMINISTRATION, General Recommendations and Concomitant Lipid-Lowering Therapy), as the risk of myopathy increases substantially at higher doses. Interruption of **simvastatin** therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

**Liver Dysfunction**  
Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1 percent of patients who received **simvastatin** in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to. . . .

In . . . one transaminase elevation to greater than 3X ULN, over the course of the study, was not significantly different between the **simvastatin** and placebo groups (14 [0.7 percent] vs. 12 [0.6 percent]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the **simvastatin** group (n equals 2,221) and 5 in the placebo group (n equals 2,223). Of the 1,986 **simvastatin** treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4 percent) developed consecutive LFT. . . abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of **simvastatin**; 37 percent were titrated to 40 mg.

The . . . have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of **simvastatin**.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with **simvastatin**. These changes appeared soon after initiation of therapy with **simvastatin**, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

**Simvastatin** may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with **simvastatin**.

**Antipyrine:** **Simvastatin** had no effect on the pharmacokinetics of antipyrine. However, since **simvastatin** is metabolized by the cytochrome P450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the. . .

**Propranolol:** In healthy male volunteers there was a significant decrease in mean C<sub>max</sub>, but no change in AUC, for **simvastatin** total and active inhibitors with concomitant administration of single doses of ZOCOR and **propranolol**. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of **propranolol** were not affected.

**Digoxin:** Concomitant administration of a single dose of digoxin in healthy male volunteers receiving **simvastatin** resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when **simvastatin** is initiated.

**Warfarin:** In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, **simvastatin** 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from. . . been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting **simvastatin** and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin. . . documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of **simvastatin** is changed or discontinued, the same procedure should be repeated. **Simvastatin** therapy has not been associated with bleeding or with changes in prothrombin time

in patients not taking anticoagulants.

Optic nerve degeneration was seen in clinically normal dogs treated with **simvastatin** for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the . . .

CNS . . . mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with **simvastatin** at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher. . .

In a 72-week carcinogenicity study, mice were administered daily doses of **simvastatin** of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8. . .

In . . . evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg **simvastatin** as measured by AUC).

In . . . significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of **simvastatin** than in humans given 80 mg **simvastatin** (as measured by AUC).

There was decreased fertility in male rats treated with **simvastatin** for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which **simvastatin** was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal. . .

**Simvastatin** was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. . .

It is not known whether **simvastatin** is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking **simvastatin** should not nurse their infants (see CONTRAINDICATIONS).

Safety . . . with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with **simvastatin** is not recommended at this time.

#### Scandinavian **Simvastatin** Survival Study

The . . . effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with **simvastatin** therapy.

In controlled clinical studies in which **simvastatin** was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with **simvastatin** or cholestyramine. The combined use of **simvastatin** with fibrates should generally be avoided (see WARNINGS, Skeletal Muscle).

The dialyzability of **simvastatin** and its metabolites in man is not known at present.

In patients taking cyclosporine concomitantly with **simvastatin** (see WARNINGS, Skeletal Muscle), therapy should begin with 5 mg of ZOCOR and should not exceed 10 mg/day.

Tablets ZOCOR (**simvastatin**) 5 mg, 10 mg, 20 mg, and 40 mg are manufactured by:

Tablets ZOCOR (**simvastatin**) 80 mg are manufactured for:

\*\*\* Manson, J.M., Freyssinges, C., Ducrocq, MB., Stephenson, W.P.,  
Postmarketing Surveillance of Lovastatin and **Simvastatin** Exposure  
During Pregnancy, Reproductive Toxicology, 10(6): 439-446, 1996.

L15 ANSWER 2 OF 192 PROMT COPYRIGHT 2001 Gale Group

#### Full-text

ACCESSION NUMBER: 1998:574057 PROMT  
TITLE: /FIRST AND FINAL ADD -- PHTH014 -- Merck & Co., Inc./.  
SOURCE: PR Newswire, (5 Nov 1998) pp. 6699.  
LANGUAGE: English  
WORD COUNT: 7280

\*FULL TEXT IS AVAILABLE IN THE ALL FORMAT\*

AB TABLETS  
ZOCOR(R)  
(**SIMVASTATIN**)  
DESCRIPTION

ZOCOR\* (**simvastatin**) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, **simvastatin**, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1alpha,3 alpha,7 beta,8 beta(2S\*,4S\*)]-8a beta]]. The empirical formula of simvastatin is C25H38O5 and its molecular weight is 418.57. Its structural formula is:

(MOLECULE HERE)

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

#### CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein (LDL) cholesterol in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL (low-density lipoprotein) cholesterol and low HDL (high-density lipoprotein) cholesterol are both risk factors for coronary heart disease. Though frequently found in association with low HDL, elevated plasma triglycerides (TG) have not been established as an independent risk factor for coronary heart disease. The independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

THIS IS AN EXCERPT: COPYRIGHT 1998 PR Newswire Association, Inc.

#### (SIMVASTATIN)

ZOCOR\* (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA).

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1alpha,3 alpha,7 beta,8 beta(2S\*,4S\*)]-8a beta]]. The empirical formula of simvastatin is C25H38O5 and its molecular weight is 418.57. Its structural formula is:

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and.

The . . . factor for coronary heart disease. The independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

THIS IS AN EXCERPT: COPYRIGHT 1998 PR Newswire Association, Inc.

#### (SIMVASTATIN)

ZOCOR\* (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA).

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1alpha,3 alpha,7 beta,8 beta(2S\*,4S\*)]-8a beta]]. The empirical formula of simvastatin is C25H38O5 and its molecular weight is 418.57. Its structural formula is:

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and.

The . . . factor for coronary heart disease. The independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with ZOCOR on total mortality was assessed in 4444 patients with.

Simvastatin is a lactone that is readily hydrolyzed in vivo to the

TX

corresponding beta -hydroxyacid, a potent inhibitor of HMG-CoA reductase..  
beta -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of 14C-labeled simvastatin in man, 13 percent of the dose was excreted in urine and 60 percent in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus 14C-metabolites) peaked at 4 hours and declined rapidly to about 10 percent of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an intravenous reference dose, in each of two animal species tested, averaged about 85 percent of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be greater than 60 percent in man), the availability of drug to the general circulation is low. In a single-dose study in nine healthy subjects, it was estimated that less than 5 percent of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48 percent for the area under the concentration-time curve.

Both simvastatin and its beta-hydroxyacid metabolite are highly bound (approximately 95 percent) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the beta-hydroxyacid of simvastatin and its 6 prime-hydroxy, 6 prime-hydroxymethyl, and 6 prime-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors. . . to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an A.H.A. recommended low-fat meal.

The results of 3 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolemia are presented in TABLE I.

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. Eleven of.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with ZOCOR on total mortality was assessed in 4444 patients with coronary heart. . . reduced by 42 percent, (p equals 0.00001, 111 vs 189). There was no statistically significant difference between groups in non- cardiovascular mortality. ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial. . .

In the Multicenter Anti-Atheroma Study, the effect of therapy with simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic men and women with coronary heart disease. In this randomized, . . . (6.4 mmol/L) and a mean baseline LDL value of 170 mg/dL (4.4 mmol/L) were treated with conventional measures and with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a. . . endpoints of the trial were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. Simvastatin significantly slowed the progression of lesions as measured in the final angiogram by both these parameters (mean changes in minimum lumen diameter: negative 0.04 mm with simvastatin vs negative 0.12 mm with placebo; mean changes in mean lumen diameter: negative 0.03 mm with simvastatin vs negative 0.08 mm with placebo), as well as by change from baseline in percent diameter stenosis (0.9 percent simvastatin vs 3.6 percent placebo). After four years, the groups also differed significantly in the proportions of patients categorized with disease progression (23 percent simvastatin vs 33 percent placebo) and disease regression (18 percent simvastatin vs 12 percent placebo). In addition, simvastatin significantly decreased the proportion of patients with new lesions (13 percent simvastatin vs 24 percent placebo) and with new total occlusions (5 percent vs 11 percent). The mean change per-patient in mean. . .

In clinical studies, **simvastatin** did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with **simvastatin**, an effect also observed with other inhibitors of HMG-CoA reductase and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled 12-week study there was no significant effect of **simvastatin** 80 mg on the plasma testosterone response to hCG. In another 24-week study **simvastatin** 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4444 patients were randomized to **simvastatin** 20-40 mg or placebo daily for a median duration of 5.4 years, the incidence of male sexual adverse events in. . .

Prior to initiating therapy with **simvastatin**, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver

**Simvastatin** and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly. . . of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely. In the Scandinavian **Simvastatin** Survival Study, there was one case of myopathy among 1399 patients taking **simvastatin** 20 mg and no cases among 822 patients taking 40 mg daily for a median duration of 5.4 years. In. . .

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. **Simvastatin** is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of **simvastatin** and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin. . .

1. General measures. Patients starting therapy with **simvastatin** should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. **Simvastatin** therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment,. . .

Of . . . patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with **simvastatin** should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. . . . reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, Drug Interactions). Physicians contemplating combined therapy with **simvastatin** and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any. . .

The combined use of **simvastatin** with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of **simvastatin** have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to **simvastatin** typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with **simvastatin**, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of **simvastatin** should generally not exceed 10 mg (see DOSAGE AND ADMINISTRATION, General Recommendations and Concomitant Lipid-Lowering Therapy), as the risk of myopathy increases substantially at higher doses. Interruption of **simvastatin** therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

Persistent . . . 3 times the upper limit of normal) in serum transaminases have occurred in approximately 1 percent of patients who received **simvastatin** in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to. . . were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the Scandinavian **Simvastatin** Survival Study (see CLINICAL PHARMACOLOGY, Clinical Studies), the number of patients with more than one transaminase elevation to greater than 3 times the upper limit of normal, over the course of the study, was not significantly different between the **simvastatin** and placebo groups (14 [0.7 percent] vs. 12 [0.6 percent]).

Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the **simvastatin** group (n equals 2,221) and 5 in the placebo group (n equals 2,223). Of the 1986 **simvastatin** treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4 percent) developed consecutive LFT elevations. . . . abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of **simvastatin**; 37 percent were titrated to 40 mg. In 2 controlled clinical studies in 1105 patients, the 12-month incidence of persistent.

The . . . have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of **simvastatin**.

As . . . moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with **simvastatin**. These changes appeared soon after initiation of therapy with **simvastatin**, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

**Simvastatin** may cause elevation of creatine kinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with **simvastatin**.

**Antipyrine:** **Simvastatin** had no effect on the pharmacokinetics of antipyrine. However, since **simvastatin** is metabolized by the cytochrome P450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the. . .

**Propranolol:** In healthy male volunteers there was a significant decrease in mean C<sub>max</sub>, but no change in AUC, for **simvastatin** total and active inhibitors with concomitant administration of single doses of ZOCOR and **propranolol**. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of **propranolol** were not affected.

**Digoxin:** Concomitant administration of a single dose of digoxin in healthy male volunteers receiving **simvastatin** resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when **simvastatin** is initiated.

**Warfarin:** In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, **simvastatin** 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from. . . been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting **simvastatin** and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin. . . documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of **simvastatin** is changed or discontinued, the same procedure should be repeated. **Simvastatin** therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Optic nerve degeneration was seen in clinically normal dogs treated with **simvastatin** for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the. . .

CNS . . . mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with **simvastatin** at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher. . .

In a 72-week carcinogenicity study, mice were administered daily doses of **simvastatin** of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8. . .

In . . . evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg **simvastatin** as measured by AUC).

In . . . significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of **simvastatin** than in humans given 80 mg **simvastatin** (as measured by AUC).

There was decreased fertility in male rats treated with **simvastatin** for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which **simvastatin** was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal. . .

**Simvastatin** was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. . .

It is not known whether **simvastatin** is excreted in human milk. Because

a small amount of another drug in this class is excreted in human milk.

women taking **simvastatin** should not nurse their infants (see CONTRAINDICATIONS).

Safety . . . with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with **simvastatin** is not recommended at this time.

#### Scandinavian **Simvastatin** Survival Study

In the Scandinavian **Simvastatin** Survival Study (4S) (see CLINICAL PHARMACOLOGY, Clinical Studies) involving 4444 patients treated with 20-40 mg/day of **ZOCOR** (n equals 2221).

The . . . effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with **simvastatin** therapy.

In controlled clinical studies in which **simvastatin** was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with **simvastatin** or cholestyramine. The combined use of **simvastatin** with fibrates should generally be avoided (see WARNINGS, Skeletal Muscle).

A . . . 450 mg. Until further experience is obtained, no specific treatment of overdosage with **ZOCOR** can be recommended. The dialyzability of **simvastatin** and its metabolites in man is not known at present.

In patients taking cyclosporine concomitantly with **simvastatin** (see WARNINGS, Skeletal Muscle), therapy should begin with 5 mg of **ZOCOR** and should not exceed 10 mg/day.

Tablets **ZOCOR** (**simvastatin**) 5 mg, 10 mg, 20 mg, and 40 mg are manufactured by:

Tablets **ZOCOR** (**simvastatin**) 80 mg are manufactured for:

\*\*\* Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of **Lovastatin** and **Simvastatin** Exposure During Pregnancy, Reproductive Toxicology, 10(6):439-446, 1996.

THIS IS THE FULL TEXT: COPYRIGHT 1998 PR Newswire Association, Inc.

L15 ANSWER 3 OF 192 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

#### Full-text

ACCESSION NUMBER: 1998-23905 DRUGU T

TITLE: Selection of drug therapy in stable angina pectoris.

AUTHOR: Savonitto S; Ardissino D

CORPORATE SOURCE: Univ.Pavia

LOCATION: Milan; Pavia, It.

SOURCE: Cardiovasc.Drugs Ther. (12, No. 2, 197-210, 1998) 3 Fig. 3

Tab. 107 Ref.

CODEN: CDTHET ISSN: 0920-3206

AVAIL. OF DOC.: Seconda Divisione Cardiologica, Ospedale Niguarda Ca' Granda, 20162 Milano, Italy. (e-mail: [ssavoni@tin.it](mailto:ssavoni@tin.it)).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AN 1998-23905 DRUGU T

AB The selection of drug therapy in stable angina pectoris is reviewed with respect to etiology of effort angina, aims of treatment, medical therapy for the prevention of mortality and major cardiac events, anti-ischemic therapy, drug selection, combination anti-ischemic therapy, silent ischemia and conduct of anti-ischemic therapy in individual patients. Drugs reported include aspirin, **simvastatin**, atenolol, metoprolol, verapamil, nifedipine, pravastatin, isradipine, propranolol, felodipine, nitroglycerin and amlodipine. Treatment of stable angina should prevent myocardial infarction, cardiac death and prevent anginal attacks. Anginal symptoms are not considered useful for selection of drug therapy. Evaluation of patients, including consideration of drug contraindications, concomitant diseases and side-effects should be combined with a more individualized approach.

ABEX The physician needs to decide whether to treat the patient with medicine or a revascularization procedure, such as PTCA or coronary artery by-pass grafting. There is no superiority of revascularization over therapy. Several prospective, randomized trials have been completed in patients with stable coronary artery disease. Lipid-lowering therapy in primary prevention of cardiac events has been confirmed. None of the anti-ischemic drugs have yet been tested enough for the potential of primary preventive effect in stable angina. Data exists on primary and secondary prevention of cardiac events in patients with hypertension and those with a recent myocardial infarction. From these studies, a primary preventive effect in stable angina may be logical, but has not been

*Alouis*



proven. Some agents have been shown to decrease anginal symptoms and increase exercise tolerance acting through multiple mechanisms. Exercise data provides useful information for selecting initial treatment. The hyperventilation test is a useful method of testing increased coronary vasomotor tone and may be helpful in the selection of initial therapy. Most patients are treated with combination treatment as combining an agent that decreases oxygen consumption with 1 that increases coronary blood flow should lead to optimal delivery, use of oxygen, raised exercise tolerance and fewer anginal symptoms. An additive effect of combination therapy is discussed. Ambulatory electrocardiographic monitoring is not necessary as a way of selecting beneficial therapy. (FD)

CT ANGINA-PECTORIS \*TR; STABLE \*TR; CARDIOPATHY \*TR; CORONARY-DISEASE \*TR; REVIEW \*FT; CASES \*FT; IN-VIVO \*FT; HYPOTENSIVE \*FT; CARDIANT \*FT; ANTIAGGREGANT \*FT

CT ANGINA-PECTORIS \*TR; STABLE \*TR; CARDIOPATHY \*TR; CORONARY-DISEASE \*TR; REVIEW \*FT; CASES \*FT; IN-VIVO \*FT; HYPOTENSIVE \*FT; CARDIANT \*FT; ANTIAGGREGANT \*FT

[02] ASPIRIN \*TR; SIMVASTATIN \*TR; PRAVASTATIN \*TR; ATENOLOL \*TR; METOPROLOL \*TR; VERAPAMIL \*TR; NIFEDIPINE \*TR; ISRADIPINE \*TR; PROPRANOLOL \*TR; FELODIPINE \*TR; NITROGLYCEROL \*TR; AMLODIPINE \*TR; TR \*FT

L15 ANSWER 4 OF 192 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 92177255 EMBASE

DOCUMENT NUMBER: 1992177255

TITLE: Lovastatin and coadministered antihypertensive/cardiovascular agents.

AUTHOR: Pool J.L.; Shear C.L.; Downton M.; Schnaper H.; Stinnett S.; Dujovne C.; Bradford R.H.; Chremos A.N.

CORPORATE SOURCE: Methodist Hospital, Mail Station F-504, 6535 Fannin Street, Houston, TX 77030, United States

SOURCE: Hypertension, (1992) 19/3 (242-248).

ISSN: 0194-911X CODEN: HPRTDN

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 006 Internal Medicine

018 Cardiovascular Diseases and Cardiovascular Surgery

030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatments. The efficacy and safety profile of lovastatin given in the presence of antihypertensive medication was evaluated using patient subgroups identified in the Expanded Clinical Evaluation of Lovastatin (EXCEL) Study. The EXCEL study examined 8,245 patients with moderate hypercholesterolemia randomly assigned either to a group treated with lovastatin (20-80 mg daily) or to a group given placebo for 48 weeks. After adjustment for patient characteristics, pairwise comparisons were made between patients taking no antihypertensive agents (n=3,772) and those taking either calcium antagonists (n=446), selective .beta.1-adrenergic receptor blockers (n=326), nonselective .beta.-adrenergic receptor blockers (n=219), potassium-sparing diuretics (n=187), thiazide diuretics (n=126), or angiotensin converting enzyme inhibitors (n=171). The placebo-corrected dose- dependent effect of lovastatin on the percent change from baseline in low- density lipoprotein cholesterol was not attenuated in any subgroup and was slightly enhanced in the calcium antagonist subgroup (-29% to -44%, p=0.06) when compared with patients taking no antihypertensive agents (-24% to -40%); this difference, however, was only of borderline significance. Patterns of lovastatin-induced increase in high-density lipoprotein cholesterol and decrease in triglycerides were not consistently different among the subgroups. Examination of mean changes in serum transaminases, mean changes in creatine kinase, and the proportion of patients discontinuing therapy for clinical adverse experiences did not indicate the presence of an interaction. In conclusion, there was no evidence for an attenuation of the lovastatin- induced changes in lipids and lipoproteins or of an alteration in the safety profile of lovastatin when administered concurrently with commonly used antihypertensive agents.

CT Medical Descriptors:

\*hypercholesterolemia: . . . level

\*antihypertensive agent: PD, pharmacology

\*antihypertensive agent: CM, drug comparison

\*antihypertensive agent: CB, drug combination

\*antihypertensive agent: IT, drug interaction

RC 6885.H8

\*antihypertensive agent: DT, drug therapy  
 \*cardiovascular agent: PD, pharmacology  
 \*cardiovascular agent: DT, drug therapy  
 \*cardiovascular agent: IT, drug interaction  
 \*cardiovascular agent: CB, drug combination  
 \*cardiovascular agent: CM, drug comparison  
 \*mevinolin: CM, drug comparison  
 \*mevinolin: IT, drug interaction  
 \*mevinolin: CB, drug combination  
 \*mevinolin: DO, drug dose  
 \*mevinolin: PD, pharmacology  
 \*mevinolin: DT, drug therapy  
 amiloride: PD, pharmacology  
 amiloride: DT, drug therapy  
 amiloride: CB, drug combination  
 amiloride: CM, drug comparison  
 amiloride: IT, drug interaction  
 atenolol: CB, drug combination  
 atenolol: CM, drug comparison  
 atenolol: DT, drug therapy  
 atenolol: IT, drug interaction  
 atenolol: PD, pharmacology  
 diltiazem: CB, drug combination  
 diltiazem: CM, drug comparison  
 diltiazem: PD, pharmacology  
 diltiazem: DT, drug therapy  
 dipeptidyl carboxypeptidase inhibitor: CM, drug comparison  
 dipeptidyl carboxypeptidase inhibitor: . . . therapy  
 labetalol: CB, drug combination  
 labetalol: PD, pharmacology  
 labetalol: DT, drug therapy  
 labetalol: IT, drug interaction  
 labetalol: CM, drug comparison  
 low density lipoprotein cholesterol: EC, endogenous compound  
 metoprolol: PD, pharmacology  
 metoprolol: IT, drug interaction  
 metoprolol: CM, drug comparison  
 metoprolol: CB, drug combination  
 metoprolol: DT, drug therapy  
 nadolol: PD, pharmacology  
 nadolol: DT, drug therapy  
 nadolol: IT, drug interaction  
 nadolol: CM, drug comparison  
 nadolol: CB, drug combination  
 nifedipine: PD, pharmacology  
 nifedipine: CB, drug combination  
 nifedipine: CM, drug comparison  
 nifedipine: IT, drug interaction  
 nifedipine: DT, drug therapy  
 propranolol: IT, drug interaction  
 propranolol: DT, drug therapy  
 propranolol: CB, drug combination  
 propranolol: PD, pharmacology  
 propranolol: CM, drug comparison  
 timolol: CB, drug combination  
 timolol: CM, drug comparison  
 timolol: IT, drug interaction  
 timolol: PD, pharmacology  
 timolol: DT, drug therapy  
 triacylglycerol: EC, endogenous compound  
 triamterene: . . .

RN (mevinolin) 75330-75-5; (amiloride) 2016-88-8, 2609-46-3; (atenolol)  
 29122-68-7; (diltiazem) 33286-22-5, 42399-41-7; (hydrochlorothiazide)  
 58-93-5; (labetalol) 32780-64-6, 36894-69-6; (metoprolol) 37350-58-6;  
 (nadolol) 42200-33-9; (nifedipine) 21829-25-4; (propranolol) 13013-17-7,  
 318-98-9, 3506-09-0, 4199-09-1, 525-66-6; (timolol) 26839-75-8;  
 (triamterene) 396-01-0; (verapamil) 152-11-4, 52-53-9

L15 ANSWER 5 OF 192 ADISNEWS COPYRIGHT 2001 (ADIS)

Full-text

ACCESSION NUMBER: 1998:289 ED: 8 Aug 2001 UP: 8 Aug 2001

DOCUMENT NUMBER: 11738324-800632111

TITLE: Symposia: Cerivastatin stabilises plaques and has few drug interactions.

TI Symposium: Cerivastatin stabilises plaques and has few drug interactions.

TX. . . atherosclerotic plaque regression, but to the stabilisation of rupture-prone atherosclerotic lesions. Administration of the new HMG CoA reductase inhibitor cerivastatin decreases the lesional concentrations of collagen-degrading enzymes and actually increases collagen levels in rupture-prone lesions. The lipid-lowering efficacy and tolerability of cerivastatin are broadly similar to those of other statins, but the drug is distinguished by a dual route of metabolic elimination. . . drug interaction profile. These factors may be points of differentiation for the agent over other available statins. A summary of cerivastatin's pharmacological and clinical effects were presented at the 13th World Congress of Cardiology [Rio de Janeiro, Brazil; April 1998].

The traditional concept of atherosclerosis is one of progressive plaque growth in the coronary arteries. . . by increasing the collagen content of unstable atherosclerotic plaques and stabilising the lesions, rather than by causing plaque regression. Administration of cerivastatin to hypercholesterolaemic rabbits with experimentally induced atherosclerotic lesions resulted in reduced accumulation of macrophages and collagen-degrading enzymes in the lesions, said Dr Libby. In addition, the collagen content of the lesions was increased, resulting in increased lesional stability. Cerivastatin is the first statin for which this type of study has been conducted.

A highly potent statin

Cerivastatin is a fully synthetic third-generation statin, and the first drug in its class to be active in sub-milligram dosages.

Cerivastatin 0.1-0.4 mg/day reduced LDL-cholesterol levels by 22-36% in patients with moderate-to-severe hypercholesterolaemia (mean baseline LDL-cholesterol levels about 200 mg/dl). . . pooled efficacy data presented by Dr Evan Stein from Medical Research Laboratories, Highland Heights, Kentucky, US. In one placebo-controlled study, cerivastatin 0.8 mg/day reduced LDL-cholesterol levels by 44% in patients with a mean baseline LDL-cholesterol level of 175 mg/dl. In contrast, LDL-cholesterol levels increased by 1.2% in placebo recipients. Thus, as with other statins, cerivastatin produced a log-linear dose-response curve. This means that there is approximately a 6% additional decrease in mean LDL-cholesterol levels for each doubling of the daily dose, with no plateau effect noted at the highest dosage yet tested [see table].

Cerivastatin therapy increases HDL-cholesterol levels by 4-8%. This effect, consistent with that of other statins, is not dose-related. The triglyceride (TG)-lowering effects of cerivastatin are dependent on the patient's baseline TG level, according to Dr Stein. Modest reductions are seen in patients with low. . . mg/dl), and larger, dose-dependent, reductions occur in patients with baseline levels > 250 mg/dl.

Efficacy comparable with other statins

The effects of cerivastatin 0.2 and 0.3 mg/day were compared with those of fluvastatin 20 and 40 mg/day in a randomised, double-blind trial conducted. . . patients initially received placebo for a 6-week, single-blind, run-in period before being randomised to treatment. After 6 weeks' therapy, recipients of cerivastatin 0.2 mg/day had significantly greater reductions in TGs and LDL- and total cholesterol levels accompanied by greater increases in HDL-cholesterol. . . with recipients of fluvastatin 20 mg/day ( $p < 0.05$  for all comparisons). After a further 6 weeks of treatment with cerivastatin 0.3 mg/day or fluvastatin 40 mg/day, cerivastatin recipients were again observed to have superior responses in all comparisons ( $p < 0.05$ ).

Good tolerability profile

According to Dr Stein, the pooled analysis data demonstrate that cerivastatin is well tolerated. The most common adverse events noted in studies with cerivastatin (headache, dyspepsia, flatulence, abdominal pain and diarrhoea) occurred in < 2% of patients, and in similar proportions for recipients of placebo and cerivastatin. The incidence of elevations in hepatic transaminase levels among cerivastatin recipients was similar to that observed with other statins.

Drug interactions unlikely

The drug-drug interaction profiles of other currently available statins are heterogeneous. Antacids, cimetidine, cyclosporin, warfarin, propranolol and digoxin, among other agents, have all been shown to interact with various statins. However, unlike other statins, cerivastatin has a dual metabolic pathway, reported Dr Wolfgang Muck of Bayer AG, Wuppertal, Germany. Cerivastatin undergoes biotransformation to 2 major metabolites via the cytochrome P450 isozymes 2C8 and 3A4. These

pathways are compensatory, allowing the elimination of cerivastatin to be relatively unaffected by the presence of competing drugs, including erythromycin, itraconazole, nifedipine, warfarin and digoxin. Additionally, cerivastatin does not affect the metabolism of these agents, he added.

Cerivastatin absorption is also unaffected by the presence of magnesium-aluminium antacids or the concomitant administration of cimetidine and omeprazole. However, cholestyramine does reduce cerivastatin absorption, but the interaction is clinically insignificant when administration of the 2 agents is separated by  $\geq 1$  hour.

Although the cerivastatin is highly bound to plasma proteins ( $> 99\%$ ), primarily albumin, its concomitant administration does not affect the pharmacokinetic profile of warfarin, nor does it alter the effects of warfarin on prothrombin time and factor VII.

Editorial Comment: Cerivastatin was launched in its first market the UK in April last year. It is now also available in several other. . . Germany, The Netherlands, Sweden and Canada, and will be launched in more than 30 countries this year.

Table. Dose-response effect of cerivastatin in patients with moderate-to- severe hypercholesterolaemia

-----	
Cerivastatin dose	Percent reduction in LDL-cholesterol levels
-----	
0.1mg (n = 384)*	-22.4
0.2mg (n = 403)*	- 28.2
0.3mg (n = . . .)	
RN 57-88-5 (CHOLESTEROL)	
81-81-2 (WARFARIN)	
114-07-8 (ERYTHROMYCIN)	
525-66-6 (PROPRANOLOL)	
9001-26-7 (PROTHROMBIN)	
9031-66-7 (TRANSAMINASE)	
11041-12-6 (CHOLESTYRAMINE)	
20830-75-5 (DIGOXIN)	
21829-25-4 (NIFEDIPINE)	
51481-61-9 (CIMETIDINE)	
73590-58-6 (OMEPRAZOLE)	
84625-61-6 (ITRACONAZOLE)	
93957-54-1 (FLUVASTATIN)	
145599-86-6 (CERIVASTATIN)	
9028-35-7Q, 37250-24-1Q (HMG-COA REDUCTASE)	
59865-13-3Q, 79217-60-0Q (CYCLOSPORIN)	

=> d ibib abs kwic 6-10

L15 ANSWER 6 OF 192 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

Full-text

ACCESSION NUMBER: 1995-43114 DRUGU T

TITLE: Beta-blockers and sudden cardiac death.

AUTHOR: Kendall M J; Lynch K P; Hjalmarson A; Kjekshus J

CORPORATE SOURCE: Univ.Oslo

LOCATION: Birmingham, U.K., Gothenburg, Swed.; Oslo, Nor.

SOURCE: Ann.Intern.Med. (123, No. 5, 358-67, 1995) 5 Fig. 2 Tab. 113

Ref.

CODEN: AIMEAS ISSN: 0003-4819

AVAIL. OF DOC.: Clinical Pharmacology Section, Department of Medicine, Queen Elizabeth Hospital, Birmingham M15 2TH, England.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AN 1995-43114 DRUGU T

AB The role of beta (b)-blockers in preventing sudden cardiac death is reviewed. Sudden cardiac death accounts for about 50% of cardiac mortality and the most common cause of cardiac death is ventricular arrhythmia as a consequence of coronary artery disease (CAD). Large, long-term trials have demonstrated consistent efficacy of b-blockers as cardioprotective agents, both alleviating myocardial ischemia and suppressing ventricular tachycardia. All b-blockers produce beneficial effects on myocardial ischemia and cardiac sympathetic activation but only the lypophilic, CNS-active b-blockers (such as timolol, propranolol and metoprolol) are cardioprotective, an effect attributed to attenuation of stress-induced vagal withdrawal; the

hydrophilic sotalol and atenolol lack efficacy.

ABEX Diuretic therapy for hypertension reduces coronary events in the elderly, but metoprolol is more effective than thiazide diuretics in reducing mortality. Aspirin and related drugs reduce post-MI mortality but not sudden cardiac death, whereas b-blockers reduce post-MI total mortality by about 20% and sudden cardiac death by 32-50%. Ca channel blockers have inconclusive or, for diltiazem, detrimental effects on mortality. ACE-inhibitors reduce post-MI cardiovascular death, but mainly in patients with impaired cardiac function, and magnesium or nitrates do not improve mortality. Animal studies indicate that some b-blockers (timolol, pindolol, propranolol, metoprolol and labetalol) increase the arrhythmia threshold. Encainide, flecainide, moricizine, quinidine and mexiletine may increase post-MI late mortality, but amiodarone appears to reduce mortality. Simvastatin is reported to reduce mortality in hypercholesterolemia/CAD. Nethalide, a b-blocker developed for hypertension, limits myocardial contractility in response to adrenalin and may cause or exacerbate CHF, but controlled studies have not demonstrated that cardioselective b-blockers increase CHF; in 1 study, metoprolol reduced use of furosemide for pulmonary edema. b-Blockers are contra-indicated in bronchospastic disease or cardiogenic shock, but are often withheld unnecessarily because of age, diabetes or CHF (where benefits may outweigh risks). Reports of adverse effects of b-blockers on well-being are generally anecdotal or unconfirmed (attributable to propranolol + methyldopa in some cases). (W2/LJ)

CT FIBRILLATION \*TR; MYOCARD.INFARCT. \*TR; CORONARY-DISEASE \*TR; VENTRICULAR \*TR; ARRHYTHMIA \*TR; CARDIOPATHY \*TR; CASES \*FT; IN-VIVO \*FT; REVIEW \*FT; CARDIOPROTECTIVE \*FT; SYMPATHOLYTIC-BETA \*FT  
[02] TIMOLOL \*TR; PROPRANOLOL \*TR; METOPROLOL \*TR; SOTALOL \*TR; ATENOLOL \*TR; PINDOLOL \*TR; LABETALOL \*TR; TR \*FT

L15 ANSWER 7 OF 192 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

Full-text

ACCESSION NUMBER: 1992-38640 DRUGU P T S

TITLE: Effects of a New Metabolic Modulator, Ranolazine, on Exercise Tolerance in Angina Pectoris Patients Treated with Beta-Blocker or Diltiazem.

AUTHOR: Cocco G; Rousseau M F; Bouvy T; Cheron P; Williams G; Detry J M

LOCATION: Rheinfelden, Switzerland; Brussels, Haine St Paul, Belgium; Leeds, United Kingdom

SOURCE: J.Cardiovasc.Pharmacol. (20, No. 1, 131-38, 1992) 2 Fig. 5 Tab. 15 Ref.

CODEN: JCPCDT ISSN: 0160-2446

AVAIL. OF DOC.: University of Louvain, avenue Hippocrate 55/5560, B-1200 Brussels, Belgium. (Pouleur H, 7 authors).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT; MPC

FILE SEGMENT: Literature

AN 1992-38640 DRUGU P T S

AB The effects of a single p.o. dose of ranolazine (RZ) were assessed in 104 patients with coronary artery disease and chronic stable angina pectoris in a double-blind, crossover, randomized, placebo-controlled study. All remained symptomatic despite treatment with diltiazem (DZ), atenolol (AT), metoprolol (ME) and propranolol (PR). Short acting nitrates, antiplatelet drugs and hypolipemic drugs (such as simvastatin) were allowed. The highest dose of RZ improved exercise duration, time to angina and time to 1 mm ST-segment depression. RZ did not affect HR or arterial pressure at rest and at peak exercise. Side effects were mild headache, dizziness and fatigue. A single dose of 240 mg RZ has an antianginal effect in patients already receiving a beta-blocker or DZ.

ABEX Methods 106 Patients (81 men; 28-73 yr, median 59) with coronary artery disease and chronic stable exercise-evoked angina receiving AT (100 mg/day), ME (200 mg/day), PR (120 mg/day) or DZ (60 mg t.i.d.) received a single p.o. dose of RZ (10, 60, 120 or 240 mg). Plasma RZ levels were measured by HPLC. Results 2 Patients were excluded. RZ (240 mg) increased exercise duration. "Intention-to-treat" analysis of time to angina showed an increase at 240 mg RZ, from 387 to 428 sec. Analysis of time to angina showed an increase on RZ (240 mg) of 56.8 sec. The effect was consistent in patients receiving DZ or beta-blockers (52 and 62 sec, respectively). Time to angina improved by at least 30 sec in 72% treated with 240 mg, 50% treated with 120 mg, 42% treated with 60 mg and 25% treated with 10 mg RZ. Time to 0.1 mV ST segment depression

increased with RZ (240 mg) by a mean of 36.5 and 43 sec when patients not achieving 0.1 min on both study days were excluded and included, respectively. RZ had no effect on resting or peak exercise HR, or systolic or diastolic B.P. values. Exercise was stopped due to angina in 54%, 62%, 59% and 32% at 10, 60, 120 and 240 mg RZ, respectively. Plasma RZ levels were higher in the DZ group than the beta-blocker group. There was a nonlinear relationship between log dose and plasma level of RZ. Angina was improved and summed ST segment depression reduced at plasma levels above 500 ng/ml. RZ induced symptoms such as mild headache, fatigue or dizziness in 22 patients. (E67/AE)

CT CHRON. \*TR; STABLE \*TR; ANGINA-PECTORIS \*TR; CARDIOPATHY \*TR;  
CORONARY-DISEASE \*TR; SIMVASTATIN \*RC; DRUG-COMPARISON \*FT; IN-VIVO  
\*FT; CASES \*FT; COMB. \*FT; RANDOM \*FT; DOUBLE \*FT; BLIND-TEST \*FT;  
CLIN.TRIAL \*FT; SYMPTOMATOLOGY \*FT; CROSSOVER. . .  
[03] ATENOLOL \*TR; SYMPATHOLYTICS-BETA \*FT; HYPOTENSIVES \*FT; ATENOLOL  
\*RN; TR \*FT  
[04] METOPROLOL \*TR; SYMPATHOLYTICS-BETA \*FT; METOPROLO \*RN; TR \*FT  
[05] PROPRANOLOL \*TR; SYMPATHOLYTICS-BETA \*FT; ANTIARRHYTHMICS \*FT;  
HYPOTENSIVES \*FT; PROPRANOLOL \*RN; TR \*FT  
[04] METOPROLOL \*TR; SYMPATHOLYTICS-BETA \*FT; METOPROLO \*RN; TR \*FT  
[05] PROPRANOLOL \*TR; SYMPATHOLYTICS-BETA \*FT; ANTIARRHYTHMICS \*FT;  
HYPOTENSIVES \*FT; PROPRANOLOL \*RN; TR \*FT  
[05] PROPRANOLOL \*TR; SYMPATHOLYTICS-BETA \*FT; ANTIARRHYTHMICS \*FT;  
HYPOTENSIVES \*FT; PROPRANOLOL \*RN; TR \*FT  
DDRN RANOLAZIN; DILTIAZEM; METOPROLOL; ATENOLOL; PROPRANOLOL

L15 ANSWER 8 OF 192 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

Full-text

ACCESSION NUMBER: 2001058475 EMBASE

TITLE: Simvastatin inhibits noradrenaline-induced hypertrophy of cultured neonatal rat cardiomyocytes.

AUTHOR: Luo J.-D.; Xie F.; Zhang W.-W.; Ma X.-D.; Guan J.-X.; Chen X.

CORPORATE SOURCE: J.-D. Luo, Department of Pharmacology, Guangzhou Medical College, Guangzhou 510182, China.  
[jlloa@public.guangzhou.gd.cn](mailto:jlloa@public.guangzhou.gd.cn)

SOURCE: British Journal of Pharmacology, (2001) 132/1 (159-164).  
Refs: 22

ISSN: 0007-1188 CODEN: BJPCBM

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB 1. Oxidative mechanisms have been implicated in neonatal cardiomyocyte hypertrophy. We and others have shown that a HMG-CoA reductase inhibitor preserves endogenous antioxidant enzyme activity and inhibits cardiac hypertrophy in vivo. We therefore have examined whether noradrenaline (NA) induces the generation of reactive oxygen species (ROS) during its induction of neonatal cardiomyocyte hypertrophy and whether simvastatin, a HMG-CoA reductase inhibitor, attenuates ROS production and thus NA-induced hypertrophy of cardiomyocytes. 2. NA increased the intracellular ROS levels in a concentration-dependent manner. This increase of ROS was significantly inhibited by simvastatin and catalase. Prazosin partially suppressed NA-induced increase of ROS and beating, while preincubation with both prazosin and propranolol completely abolished NA-evoked increase of ROS and beating. Simvastatin did not affect NA-induced increase of beating. 3. The NA-induced increase of protein content was partially suppressed by prazosin and completely abolished by preincubation with both prazosin and propranolol. Simvastatin inhibited the increase of NA-induced increase of RNA content and [(3)H]-leucine incorporation in a concentration-dependent manner. Mevalonic acid (MVA) reversed the inhibition of NA-induced RNA and protein increase by simvastatin. Catalase also inhibited the NA-induced increase of RNA and protein. 4. We conclude that the inhibitory effects of simvastatin on myocyte hypertrophy were associated with its antioxidant effects and inhibition of MVA-metabolism pathway in neonatal rat cardiomyocytes. NA-induced increases of intracellular ROS and cardiomyocyte hypertrophy requires both  $\alpha$  and  $\beta$  adrenoceptors activation in neonatal rat cardiomyocytes. The increases of ROS induced by NA is required for hypertrophy.

RN (simvastatin) 79902-63-9; (noradrenalin) 1407-84-7, 51-41-2; (catalase) 9001-05-2; (prazosin) 19216-56-9, 19237-84-4; (propranolol) 13013-17-7,

318-98-9, 3506-09-0, 4199-09-1, 525-66-6; (RNA) 63231-63-0; (leucine)  
61-90-5, 7005-03-0; (mevalonic acid) 150-97-0

L15 ANSWER 9 OF 192 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

Full-text

ACCESSION NUMBER: 2001-36589 DRUGU P S  
TITLE: Colesevelam hydrochloride: a novel bile acid-binding resin.  
AUTHOR: Aldridge M A; Ito M K  
CORPORATE SOURCE: Univ.Pacific  
LOCATION: Stockton; San Diego, Cal., USA  
SOURCE: Ann.Pharmacother. (35, No. 7-8, 898-907, 2001) 1 Fig. 5 Tab.  
37 Ref.

CODEN: APHRER ISSN: 1060-0280

AVAIL. OF DOC.: Department of Pharmacy (119), VA San Diego Health Care  
System, 3350 La Jolla Village Dr. 119, San Diego, CA  
92161-0001, U.S.A. (M.K.I.). (e-mail: [uopito@aol.com](mailto:uopito@aol.com)).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AN 2001-36589 DRUGU P S

AB The effects of colesevelam hydrochloride are reviewed. The pharmacology, pharmacokinetic/pharmacodynamics, and clinical studies on colesevelam are discussed. Colesevelam monotherapy and combination therapy with simvastatin, atorvastatin, and lovastatin are considered. The safety profile of colesevelam and its drug interactions with digitalis, glycosides, digoxin, warfarin, valproic acid, quinidine, metoprolol, lovastatin, and verapamil are described. Therapeutic and economic issues and formulary recommendation on the use of colesevelam are explained. HMG-CoA reductase inhibitors are the drugs of choice for patients with primary hypercholesterolemia since these medications are the most efficacious in reducing LDL cholesterol, are well tolerated, and reduced cardiovascular morbidity and mortality.

ABEX Colesevelam has a high affinity to dihydroxy and trihydroxy bile acids in the intestine, which increases fecal bile acid secretion reducing the enterohepatic circulation of bile acids. Colesevelam has better bile acid-binding activity compared with currently available bile acid-binding resins. Mean maximum whole blood equivalent concentration of colesevelam is 0.17 ug Eq/ml at 72 hr after a dose. The peak effect of colesevelam occurs during the 1st 2 wk of therapy when LDL cholesterol concentrations drop rapidly. Combination therapy produces at least an additive effect over monotherapy with either colesevelam or lovastatin. Colesevelam plus simvastatin reduces LDL cholesterol and increases HDL cholesterol. Colesevelam plus atorvastatin is not different from atorvastatin (80 mg/day) in terms of percent change in LDL cholesterol. Colesevelam is well-tolerated, and does not change hematologic parameters, concentrations of vitamins E and A, partial thrombin or prothrombin time, estradiol concentrations, body weight, systolic, and diastolic B.P., or HR. Colesevelam has no effect on the bioavailability of digitalis, glycosides, warfarin, valproic acid, quinidine, metoprolol, and lovastatin. Digitalis, glycosides, warfarin, valproic acid, quinidine, metoprolol and lovastatin decrease the Cmax and AUC of sustained release verapamil by 31 and 11%, respectively. Colesevelam is 2-4 times more potent on a gram-to-gram basis than cholestyramine and colestipol. Colesevelam has a favourable pharmacokinetic profile and appears to have no effect on the bioavailability of digoxin, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. (MLM/LL)

L15 ANSWER 10 OF 192 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD

Full-text

ACCESSION NUMBER: 1998-13427 DRUGU T B S E  
TITLE: Secondary prevention therapy in patients with coronary artery disease.  
AUTHOR: Dhond M; Amsterdam E A  
CORPORATE SOURCE: Univ.California  
LOCATION: Sacramento, Cal., USA  
SOURCE: Formulary (33, No. 2, 120-36, 1998) 1 Fig. 5 Tab. 62 Ref.  
CODEN: FORMF ISSN: 1082-801X

AVAIL. OF DOC.: Division of Cardiovascular Medicine, 4150 V St, Suite 3500,  
Sacramento, CA 95817, U.S.A. (E.A.A.).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AN 1998-13427 DRUGU T B S E

- AB Secondary prevention therapy in patients with coronary artery disease (CAD) is reviewed with reference to risk factor modification, **cardioprotective** drug therapy and myocardial revascularization. Risk factor modifications include lipid reductions, hypertension treatment, diabetes, hormone replacement therapy, cigarette smoking and exercise. **Cardioprotective** drug therapies include antiplatelet/anticoagulant agents (aspirin, ticlopidine, clopidogrel bisulfate, warfarin), beta blockers, ACE inhibitors, nitrates (isosorbide mononitrate), calcium channel blockers (diltiazem, verapamil) and vitamin E. Revascularization is achieved by percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass surgery (CABG). Secondary prevention by risk factor modification and by drugs established as **cardioprotective** is highly effective in reducing coronary events.
- ABEX The cornerstone of lipid-lowering therapy is dietary modification which should be maintained even if antihyperlipidemic drugs are required. The most effective agents are the HMG CoA reductase inhibitors, or statins, which block the rate-limiting step in hepatic cholesterol synthesis. Such drugs include fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin and cerivastatin. Side-effects are relatively rare with these drugs. Estrogen replacement therapy in postmenopausal women augments HDL cholesterol, while greater increases have been achieved with gemfibrozil and nicotinic acid. Nicotinic acid, however, has been associated with side-effects, including flushing. The fibrate group, including gemfibrozil, clofibrate, bezafibrate and fenofibrate reduce triglycerides and LDL cholesterol and increase HDL cholesterol and are generally well tolerated. Cholestyramine and colestipol bind salts in the gut which leads to increased receptor-mediated uptake of LDL cholesterol from plasma. Both systolic and diastolic hypertension are risk factors for CAD. B.P. control can be achieved with numerous agents. Diabetes is another risk factor for CAD. Glycemic control is achieved through diet, exercise, oral hypoglycemic agents, insulin or combined drug therapy. Beta-blockers block beta-1 and beta-2 receptors in the heart, lung and peripheral vasculature and include metoprolol, atenolol, propranolol, nadolol, labetalol, sotalol and acebutolol. ACE inhibitors inhibit angiotensin-converting enzyme, thereby preventing the formation of angiotensin II, a potent vasoconstrictor. (E161/ECB)
- CT CORONARY-DISEASE \*TR; CARDIOPATHY \*TR; ARTERIOSCLEROSIS \*TR; VASCULAR-DISEASE \*TR; IN-VIVO \*FT; CASES \*FT; REVIEW \*FT; RISK-FACTOR \*FT; LOW \*FT; DENSITY \*FT; HIGH \*FT; LIPOPROTEIN. . .
- CT CORONARY-DISEASE \*TR; CARDIOPATHY \*TR; ARTERIOSCLEROSIS \*TR; VASCULAR-DISEASE \*TR; IN-VIVO \*FT; CASES \*FT; REVIEW \*FT; RISK-FACTOR \*FT; LOW \*FT; DENSITY \*FT; HIGH \*FT; LIPOPROTEIN. . .
- [02] ASPIRIN \*TR; TICLOPIDINE \*TR; CLOPIDOGREL-BISULFATE \*TR; WARFARIN \*TR; ISOSORBIDE-MONONITRATE \*TR; DILTIAZEM \*TR; VERAPAMIL \*TR; TOCOPHEROL \*TR; FLUVASTATIN \*TR; LOVASTATIN \*TR; PRAVASTATIN \*TR; SIMVASTATIN \*TR; ATORVASTATIN \*TR; CERIVASTATIN \*TR; GEMFIBROZIL \*TR; NICOTINATE \*TR; CLOFIBRATE \*TR; BEZAFIBRATE \*TR; FENOFIBRATE \*TR; COLESTYRAMINE \*TR; COLESTIPOL \*TR; INSULIN \*TR; METOPROLOL \*TR; ATENOLOL \*TR; PROPRANOLOL \*TR; NADOLOL \*TR; LABETALOL \*TR; SOTALOL \*TR; ACEBUTOLOL \*TR; CAPTOPRIL \*TR; ENALAPRIL-MALEATE \*TR; ENALAPRILAT \*TR; RAMIPRIL \*TR; TRANDOLAPRIL \*TR; BENAZEPRIL. . . \*FT
- [03] ASPIRIN \*AE; TICLOPIDINE \*AE; CLOPIDOGREL-BISULFATE \*AE; WARFARIN \*AE; ISOSORBIDE-MONONITRATE \*AE; DILTIAZEM \*AE; VERAPAMIL \*AE; TOCOPHEROL \*AE; FLUVASTATIN \*AE; LOVASTATIN \*AE; PRAVASTATIN \*AE; SIMVASTATIN \*AE; ATORVASTATIN \*AE; CERIVASTATIN \*AE; GEMFIBROZIL \*AE; NICOTINATE \*AE; CLOFIBRATE \*AE; BEZAFIBRATE \*AE; FENOFIBRATE \*AE; COLESTYRAMINE \*AE; COLESTIPOL \*AE; INSULIN \*AE; METOPROLOL \*AE; ATENOLOL \*AE; PROPRANOLOL \*AE; NADOLOL \*AE; LABETALOL \*AE; SOTALOL \*AE; ACEBUTOLOL \*AE; CAPTOPRIL \*AE; ENALAPRIL-MALEATE \*AE; ENALAPRILAT \*AE; RAMIPRIL \*AE; TRANDOLAPRIL \*AE; BENAZEPRIL. . .
- [03] ASPIRIN \*AE; TICLOPIDINE \*AE; CLOPIDOGREL-BISULFATE \*AE; WARFARIN \*AE; ISOSORBIDE-MONONITRATE \*AE; DILTIAZEM \*AE; VERAPAMIL \*AE; TOCOPHEROL \*AE; FLUVASTATIN \*AE; LOVASTATIN \*AE; PRAVASTATIN \*AE; SIMVASTATIN \*AE; ATORVASTATIN \*AE; CERIVASTATIN \*AE; GEMFIBROZIL \*AE; NICOTINATE \*AE; CLOFIBRATE \*AE; BEZAFIBRATE \*AE; FENOFIBRATE \*AE; COLESTYRAMINE \*AE; COLESTIPOL \*AE; INSULIN \*AE; METOPROLOL \*AE; ATENOLOL \*AE; PROPRANOLOL \*AE; NADOLOL \*AE; LABETALOL \*AE; SOTALOL \*AE; ACEBUTOLOL \*AE; CAPTOPRIL \*AE; ENALAPRIL-MALEATE \*AE; ENALAPRILAT \*AE; RAMIPRIL \*AE; TRANDOLAPRIL \*AE; BENAZEPRIL. . .